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A.M.A. ARCHIVES OF

DERMATOLOGY

The Disease Called "Wildfire"
Clement E. Counter

Extramammary Paget's Disease with Metastasis to Lymph Nodes
Philip H. Prose and Arthur B. Hyman

Use of Relaxin in Management of Ulceration and Gangrene Due to Collagen Disease
Hugh Reynolds and Clarence S. Livingood

Cutaneous Meningioma (Psammoma)
T. K. Shnitka and G. O. Bain

Ichthyosis Follicularis
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Growth and Development
Carrell P. Horton and E. Perry Crump

Ionizing Radiations in Industry
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Long-Term Triamcinolone Therapy of Alopecia Universalis
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Amphotericin as a Topical Antifungal Antibiotic
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Treponemal Tests on Cerebrospinal Fluid
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The P-Toluene Sulfonic Acid Test for Systemic Lupus Erythematosus
Joel R. Barkoff and Faye Sawyer

Pathological Changes Associated with Aluminum and Zirconium Compounds
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Intermediary Metabolism of Phenylalanine and Tyrosine in Diffuse Collagen Diseases
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Reports: Standards and Minimum Requirements for a Dermatologic Service
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Pemphigus Vulgaris and Diabetes Mellitus
Robert H. Harris and Fred Taylor Jr.

A Curious Foreign-Body Tumor
Joseph V. Klauder

Antimycotic Cream and Powder
Eugene S. Bereston

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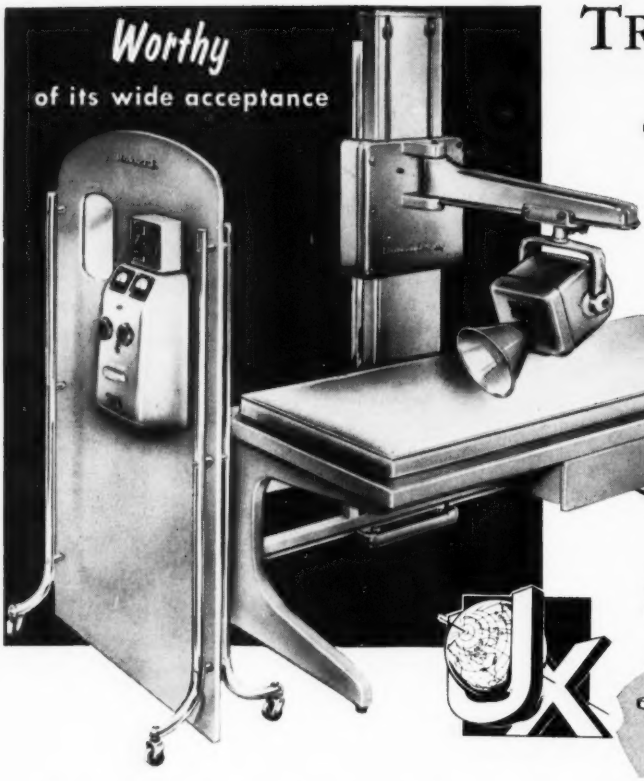

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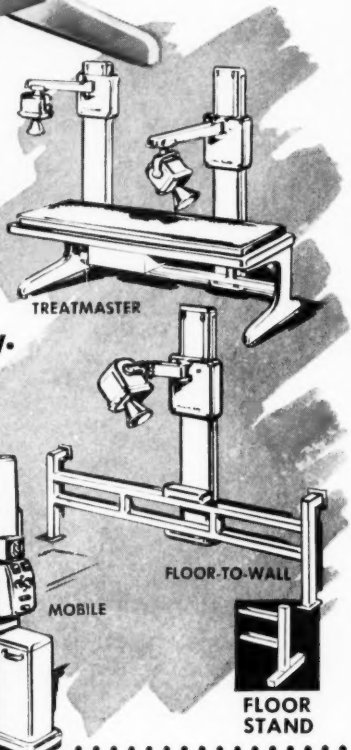

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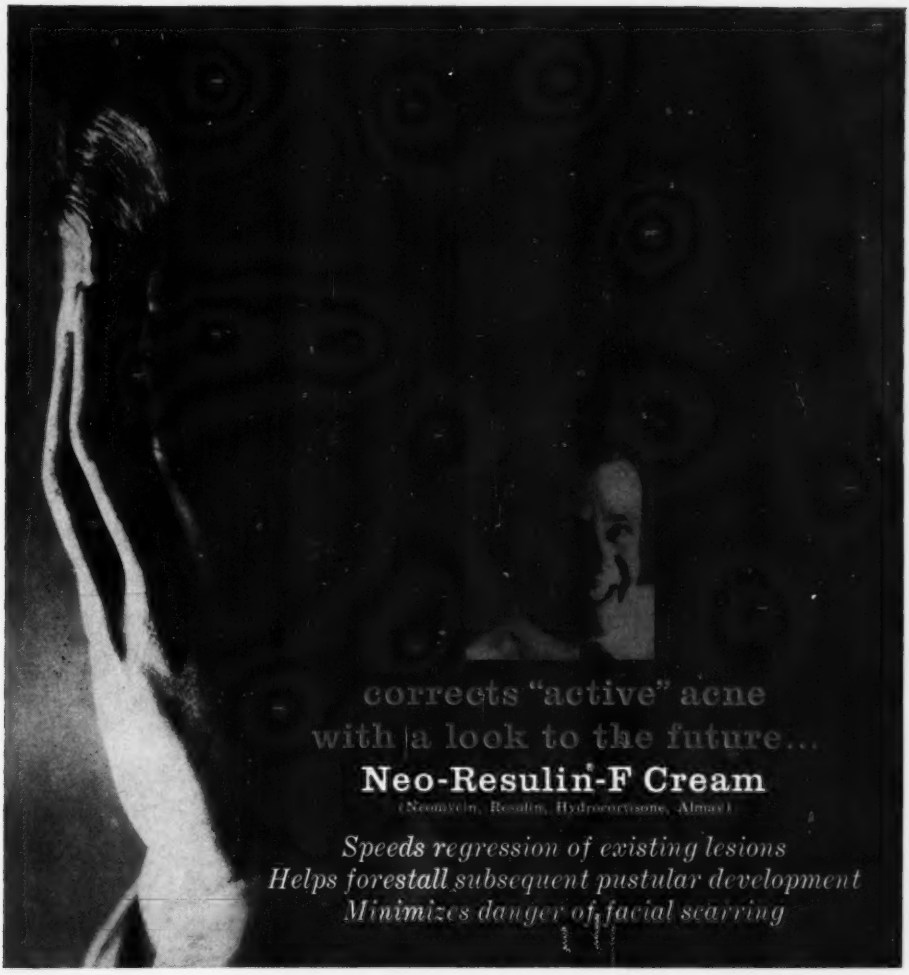
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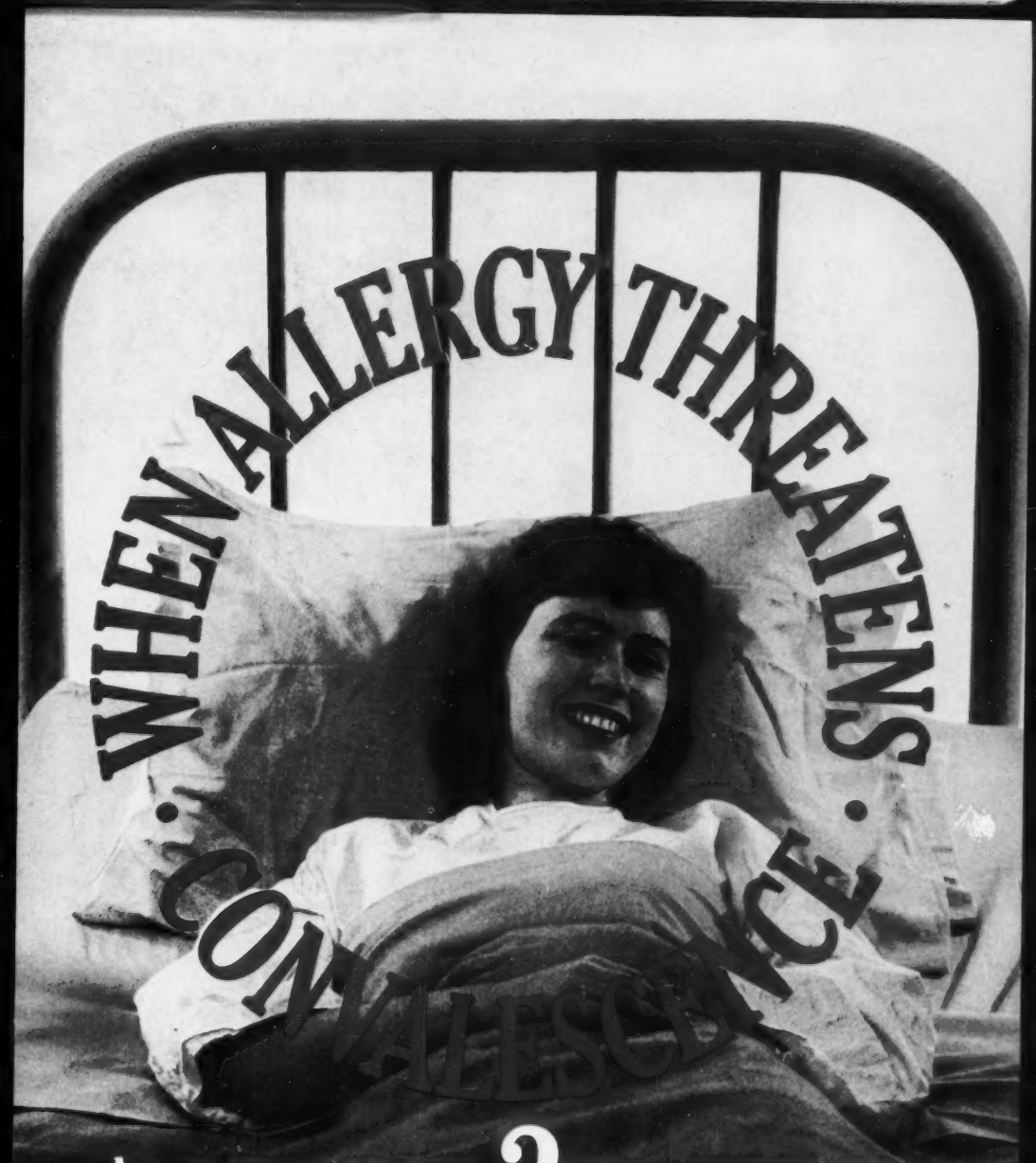

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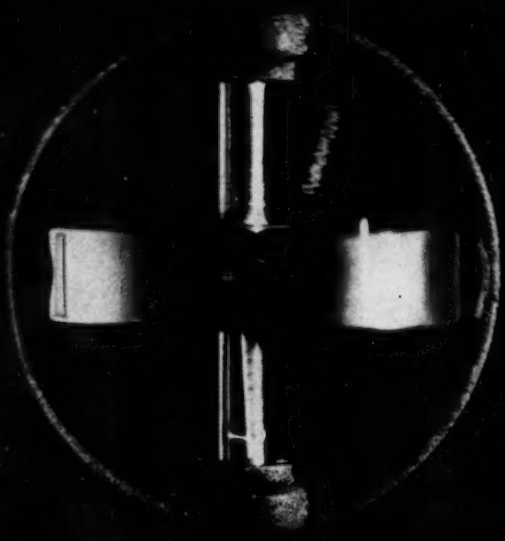

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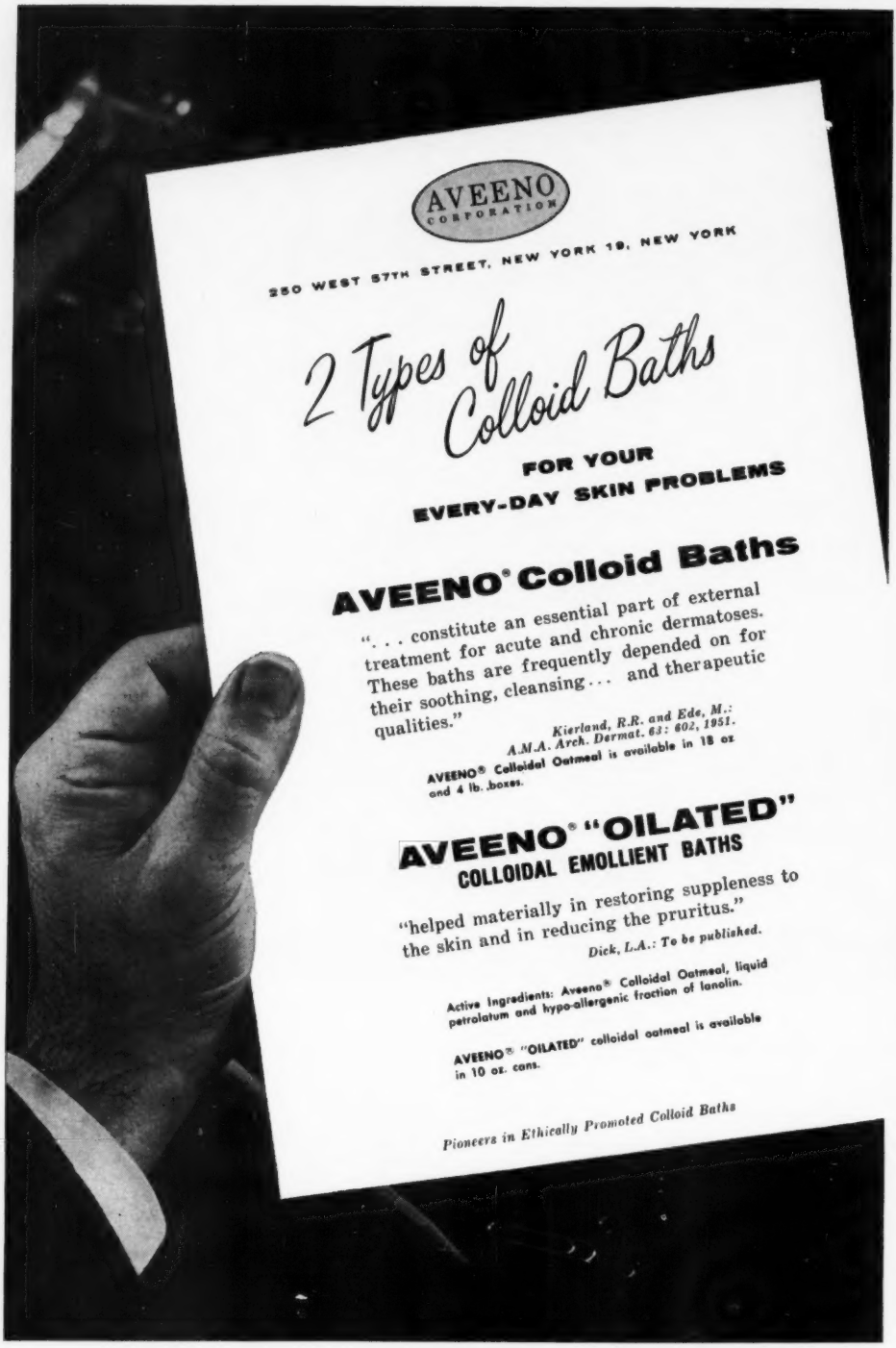
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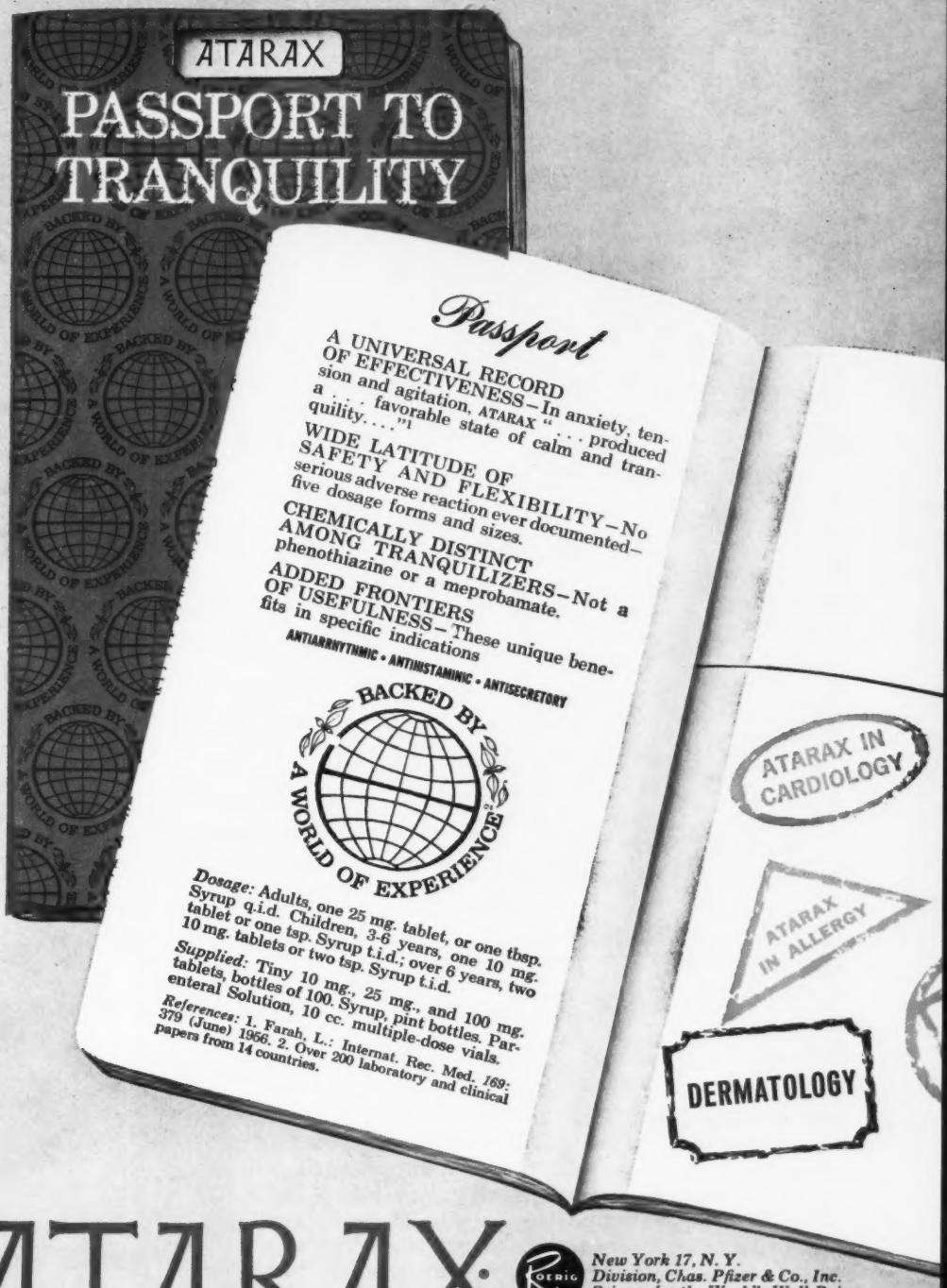
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PASSPORT TO TRANQUILITY
Passport
A UNIVERSAL RECORD OF EFFECTIVENESS—In anxiety, tension and agitation, ATARAX "... produced a ... favorable state of calm and tranquility...."1
WIDE LATITUDE OF SAFETY AND FLEXIBILITY—No serious adverse reaction ever documented—five dosage forms and sizes.
CHEMICALLY DISTINCT AMONG TRANQUILIZERS—Not a phenothiazine or a meprobamate.
ADDED FRONTIERS OF USEFULNESS—These unique benefits in specific indications
ANTIARRHYTHMIC • ANTIHISTAMINIC • ANTISECRETORY
BACKED BY A WORLD OF EXPERIENCE
Dosage: Adults, one 25 mg. tablet, or one tbsp. Syrup q.i.d. Children, 3-6 years, one 10 mg. tablet or one tsp. Syrup t.i.d.; over 6 years, two 10 mg. tablets or two tsp. Syrup t.i.d.
Supplied: Tiny 10 mg., 25 mg., and 100 mg. tablets, bottles of 100. Syrup, pint bottles. Parenteral Solution, 10 cc. multiple-dose vials.
References: 1. Farah, L.: Internat. Rec. Med. 169: 379 (June) 1956. 2. Over 200 laboratory and clinical papers from 14 countries.
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What makes Ivory Soap so pure...something that goes into it, or something that's left out?

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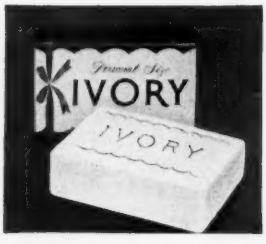

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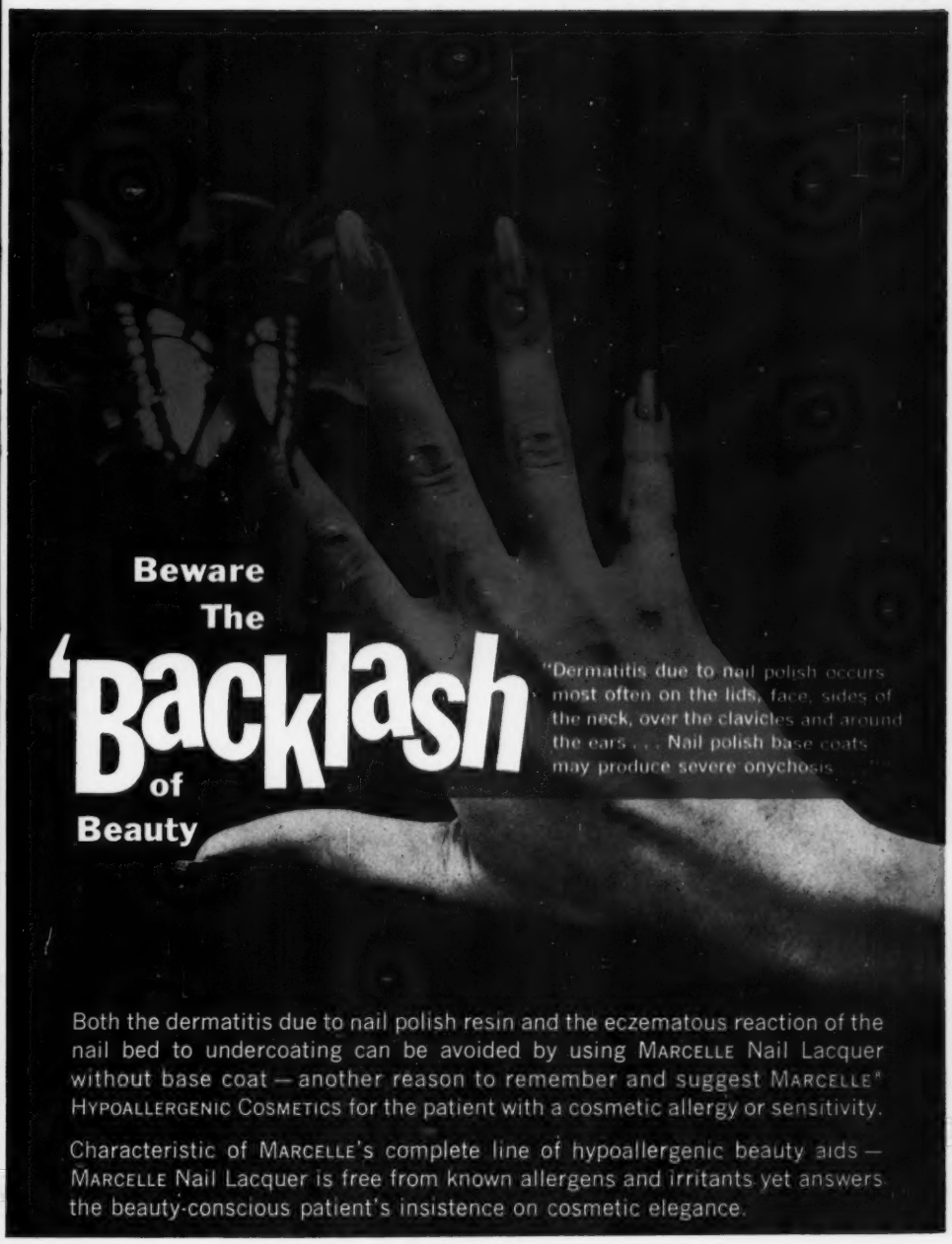
Beware
The
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of
Beauty
"Dermatitis due to nail polish occurs most often on the lids, face, sides of the neck, over the clavicles and around the ears . . . Nail polish base coats may produce severe onychosis."

Both the dermatitis due to nail polish resin and the eczematous reaction of the nail bed to undercoating can be avoided by using MARCELLE Nail Lacquer without base coat — another reason to remember and suggest MARCELLE* HYPOALLERGENIC COSMETICS for the patient with a cosmetic allergy or sensitivity.

Characteristic of MARCELLE's complete line of hypoallergenic beauty aids — MARCELLE Nail Lacquer is free from known allergens and irritants yet answers the beauty-conscious patient's insistence on cosmetic elegance.

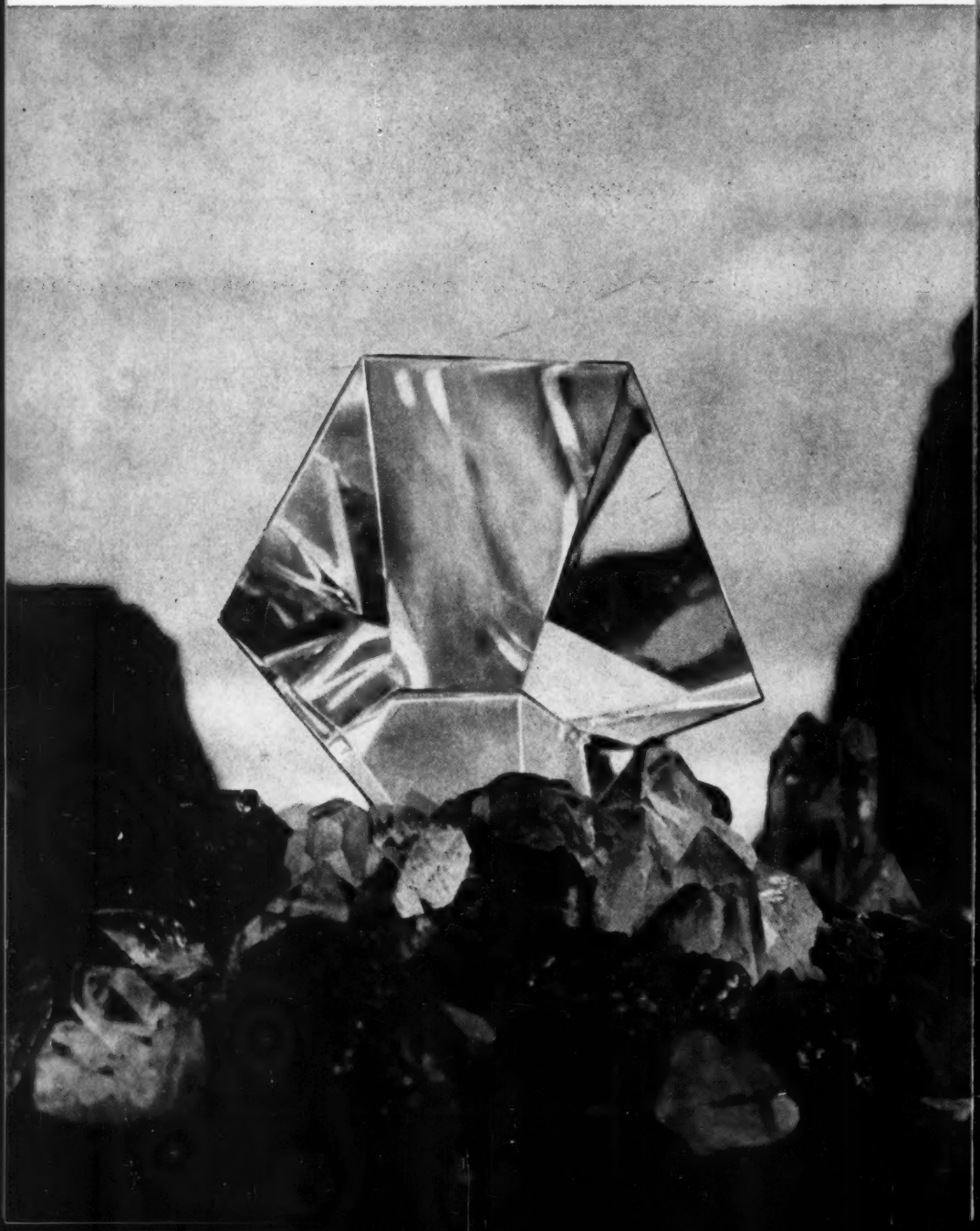
Marcelle COSMETICS

Borden's PHARMACEUTICAL DIVISION
350 Madison Avenue, New York 17

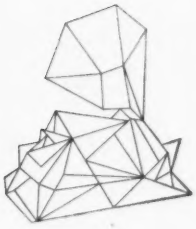
Available in Canada through Prof. Sales Corp., Montreal

*Andrews, G. C.: Diseases of the Skin, ed. 4, Philadelphia, Saunders, 1954, pp. 117, 118

PURE ANTIHISTAMINE ACTION
A PHARMACOLOGIC FACT
BECAUSE DĪSOMER
SHEDS THE MOLECULAR DROSS



NEW...IN THE TREATMENT OF ALLERGIC DISORDERS



- *"...high therapeutic index"*[1]
- *unsurpassed clinical efficacy*
- *highly effective in exceptionally small doses*
- *side effects reduced to minimal level*

Disomer....a scientific contribution in the pharmacology of antihistamines!

Incorporating the newest knowledge of structure-function relationships, DISOMER comes close to the therapeutic ideal of pure antihistamine activity. DISOMER represents the *d*-isomer of racemic brompheniramine maleate. In shedding the *l*-isomer a high point in clinical effectiveness is achieved while side effects are reduced to a minimal level.

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With DISOMER your allergic patient remains your alert patient while enjoying unsurpassed freedom from allergic symptoms. Ready now for your prescription—DISOMER is available in a variety of dosage forms to fit your patients' individual requirements.

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DISOMER CHRONOTAB*	4 mg.
DISOMER Tablets	2 mg.
DISOMER Syrup	2 mg. per 5 cc.

Usual dosage:

6 mg. CHRONOTAB	b.i.d.
4 mg. CHRONOTAB	t.i.d.
2 mg. Tablet	q.i.d.
Syrup 1 teaspoonful	q.i.d.

**Chronotab* *is White's repeat-action tablet.*

References: (1) Gould, A. H. and Long, D. L.: Clinical Pharmacology and Therapeutic Use of Dexbrompheniramine Maleate (Disomer), a new Histamine Antagonist (submitted for publication). (2) Medical Department, White Laboratories, Inc.

WHITE LABORATORIES, INC.
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...sheds the molecular dross

In eczematous dermatitis with secondary infection CREME AND LOTION pH 5.0

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HYDROCORTISONE • STAINLESS TAR • DIIODOHYDROXYQUINOLINE
IN ALUMINUM ACETATE VEHICLE

COR-TAR-QUIN is especially effective in those dermatoses where an inflammatory reaction is accompanied by increased scaling, lichenification, and secondary infection.

Combined hydrocortisone-coal tar therapy produces an enhanced antipruritic, anti-inflammatory response and diiodohydroxyquinoline is fungicidal as well as bactericidal. The Acid Mantle creme base of COR-TAR-QUIN helps restore and maintain normal pH of the skin. Relief is prompt and lasting.

Sig: Apply b.i.d. ½ oz., 2 oz., and 4 oz. tubes with either 0.5% or 1.0% hydrocortisone

INCORPORATED IN EXCLUSIVE ACID MANTLE® VEHICLE

also available without the stainless tar, as CORT-QUIN™ CREME pH 4.5

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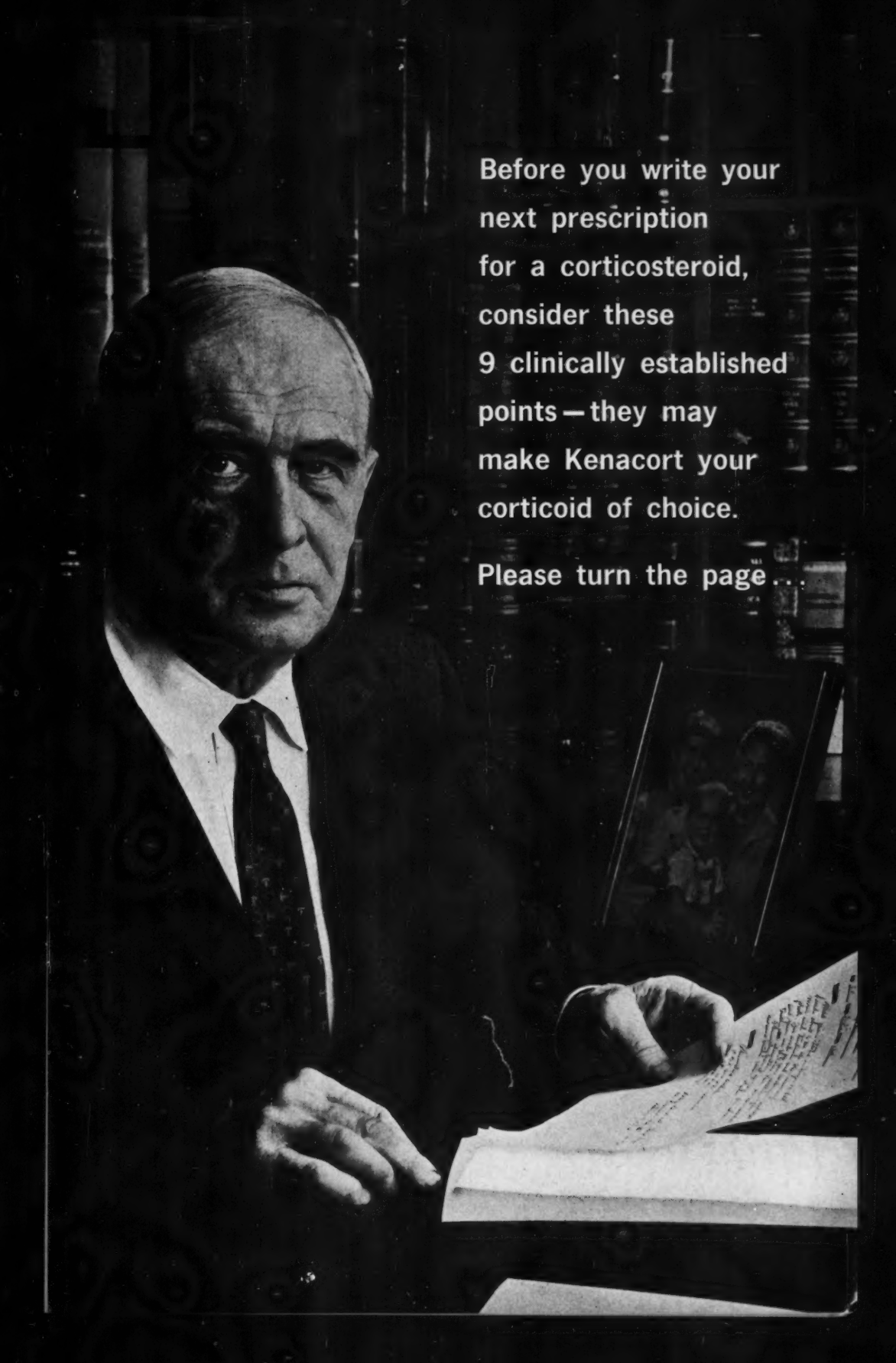
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pre-prescription point number **1**

initial therapy—remarkably free from complications

Allison, J. R., Sr., and Allison, J. R., Jr.: Monographs on Therapy 3:99 (Oct.) 1958.

pre-prescription point number **2**

continuing therapy—maintenance doses are low

Feinberg, S. M.; Feinberg, A. R., and Fisherman, E. W.: J. A. M. A. 167:58 (May 3) 1958.

pre-prescription point number **3**

no sodium or water retention—low salt diet not necessary

Hartung, E. F.: J. A. M. A. 167:973 (June 21) 1958.

pre-prescription point number **4**

absence of edema

Council on Drugs: J. A. M. A. 169:257 (Jan. 17) 1959.

pre-prescription point number **5**

less likely to create electrolyte disturbance

Bongiovanni, A. M.; Mellman, W. J., and Eberlein, W. R.: J. Pediat. 53:3 (July) 1958.

pre-prescription point number **6**

no secondary hypertension—no significant change in pulse, respiration, or blood pressure

Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.: J. A. M. A. 167:959 (June 21) 1958.

Bernsten, C. A., Jr., and others: New York Rheumatism Association, Annual Meeting, New York, April 9, 1959.

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(SQUIBB TRIAMCINOLONE)

Available in 1 mg., 2 mg., and 4 mg. scored tablets.

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Squibb Quality — the Priceless Ingredient

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no excessive appetite

Council on Drugs:
J. A. M. A. 169:257 (Jan. 17) 1959.

pre-prescription point number **8**

without unnatural psychic stimulation —does not stimulate and rarely depresses the mood

Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.:
J. A. M. A. 167:959 (June 21) 1958.
Council on Drugs:
J. A. M. A. 169:257 (Jan. 17) 1959.

pre-prescription point number **9**

gastrointestinal complaints infrequent

Hartung, E. F.:
J. A. M. A. 167:973 (June 21) 1958.

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now "a fundamentally new therapeutic approach"[1]

in fungous infections of skin, hair and nails

oral fulvicin*

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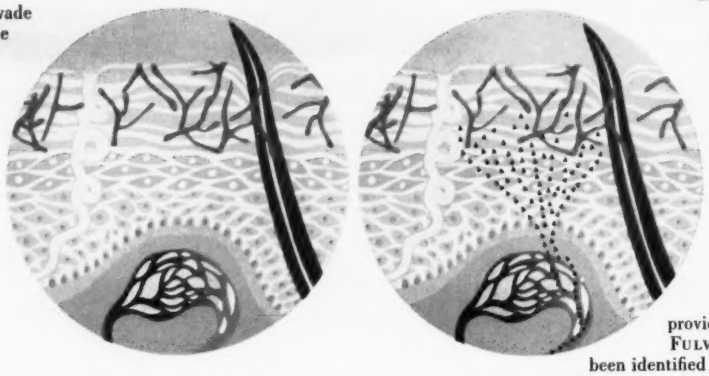
FIRST EFFECTIVE PENETRATION OF KERATIN—FROM THE INSIDE

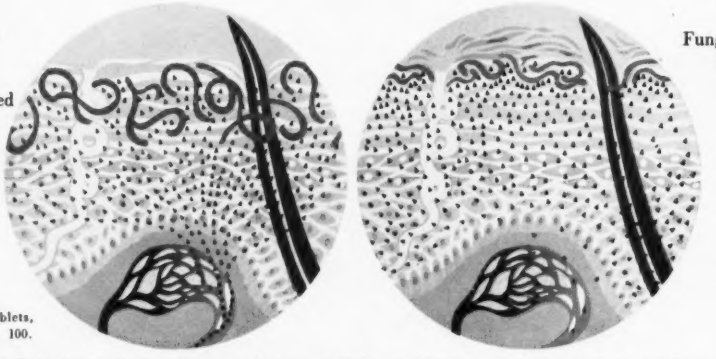
Pathogenic fungi invade and proliferate in the stratum corneum (and also in keratinized part of nails and hair), where they are usually inaccessible to treatment from the outside by topical antifungal agents, even with the aid of keratolytics.



Following oral administration, FULVICIN is absorbed and incorporated in newly growing dermal cells. As these cells approach the surface and become keratinized, they retain sufficient amounts of FULVICIN to provide fungistasis. FULVICIN has also been identified in hair shafts in fungistatic concentrations.[2]

"CURLING FACTOR" INHIBITS FUNGAL GROWTH —PERMITS OUTGROWTH OF HEALTHY TISSUE

Hyphal (filamental) tips of fungi are curled, contorted and stunted by FULVICIN.[3] Growth ceases, further penetration of keratin halts, and the fungal disease is arrested.



Fungus inhibited by FULVICIN is cast off as keratin grows out and sloughs off. Healthy tissue replaces infected keratin of skin, hair or nails.

Packaging: FULVICIN Tablets, 250 mg., bottles of 30, 100.

References: (1) Williams, D. I.; Marten, R. H., and Sarkany, I.: Lancet *2*:1212, 1958. (2) Gentles, J. C.; Barnes, M. J., and Fantes, K. H.: Nature *183*:256, 1959. (3) Brian, P. W.; Curtis, P. J., and Hemming, H. G.: Tr. Brit. Mycol. Soc. *29*:173, 1946.

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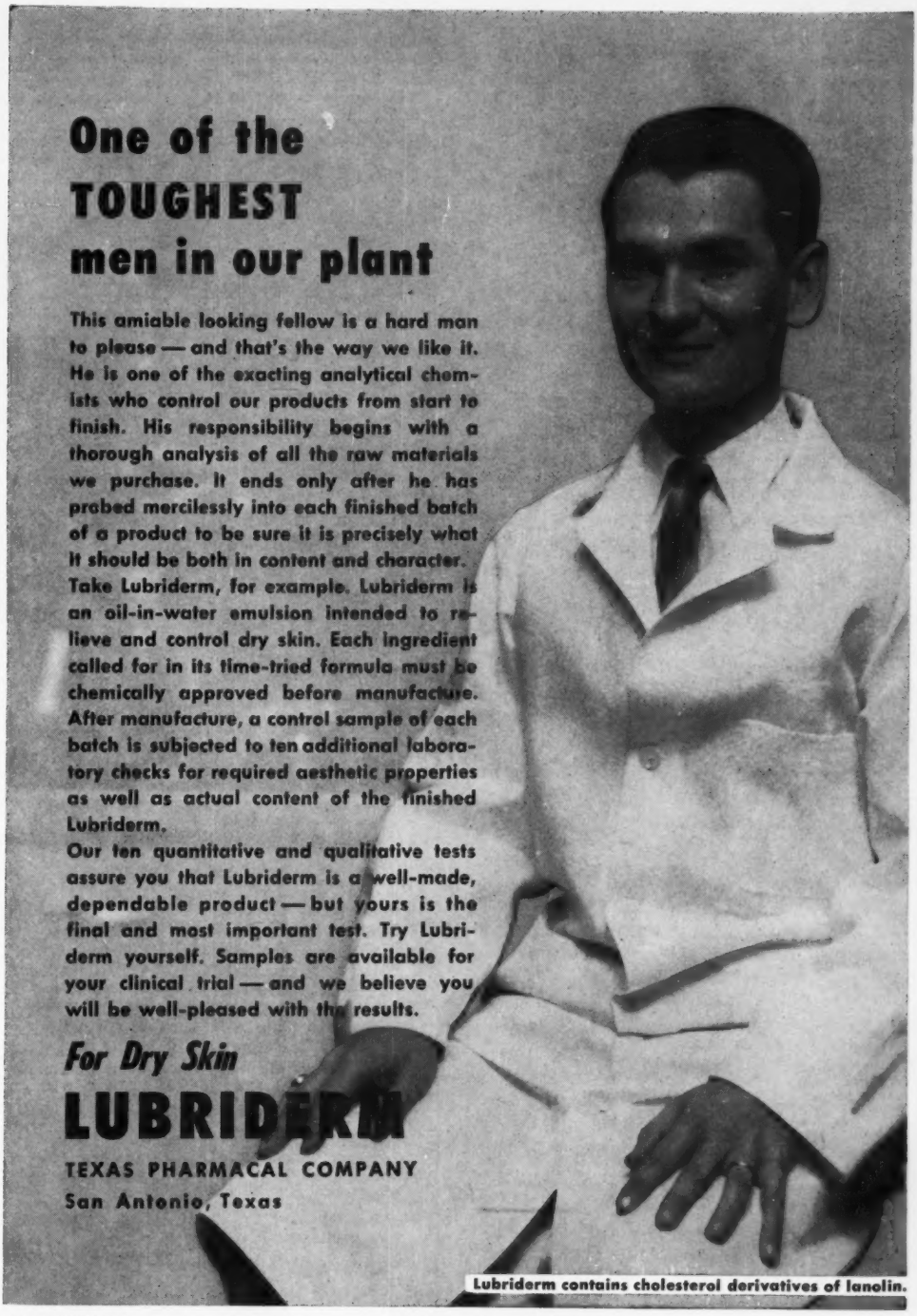
*T.M.

9-236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Lubriderm contains cholesterol derivatives of lanolin.

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SHAMPOO

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Removes ointments and medications gently but thoroughly.

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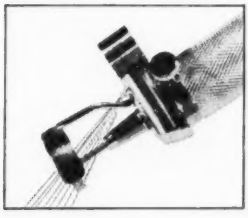

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**A.M.A. Archives of Dermatology, April 1955*
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doctor,

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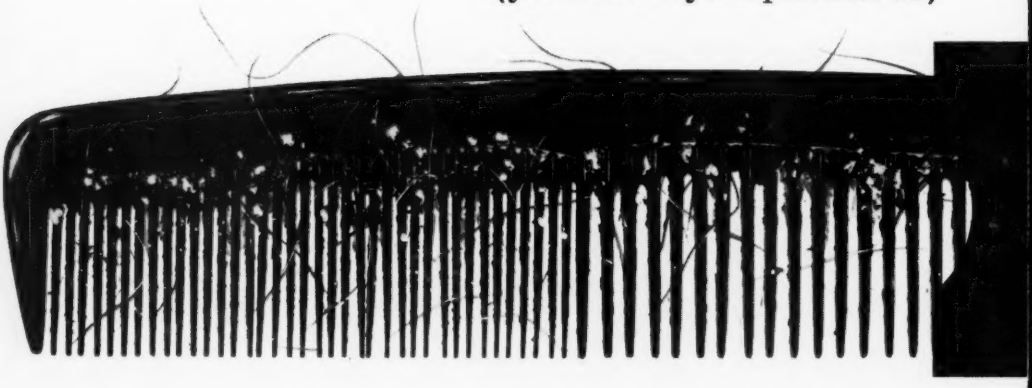
(yet some of your patients do)



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- *effectiveness*—"Of eighty-four patients . . . seventy-nine [94%] obtained good to excellent results."[3]

THEIR PATIENTS SAY:

- *cosmetically acceptable and easy-to-use*—"This product is remarkably well accepted by the patients as an excellent, foamy shampoo, free from any objectionable odor . . ."[4]

Capsebon is available on prescription only.

References: 1. Harvey, J. H., and Ereaux, L. P.: Clinical study of cadmium sulfide shampoo, Canad. M.A.J. *79*:917 (Dec. 1) 1958. 2. Stough, D. B.; Lewis, R. A.; Farmer, B. L.; Osment, L. S., and Noojin, R. O.: New beneficial agents in the treatment of acne vulgaris and seborrheic dermatitis, Postgrad. Med. *24*:439 (Oct.) 1958. 3. Kirby, W. L.: Preliminary and short report: Cadmium sulfide shampoo in seborrhea capitis, J. Invest. Dermat. *29*:159 (Sept.) 1957. 4. Mullins, J. F., and Barnett, J. R.; Cadmium shampoo treatment of seborrheic dermatitis, Texas J. Med. *53*:640 (Aug.) 1957.

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1% CADMIUM SULFIDE SUSPENSION

a dandruff treatment that isn't a "waste of time"

to control dandruff with Capsebon

1. The patient should thoroughly shampoo with Capsebon or his usual cosmetic shampoo.
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Supplied: In 4-ounce plastic bottles.

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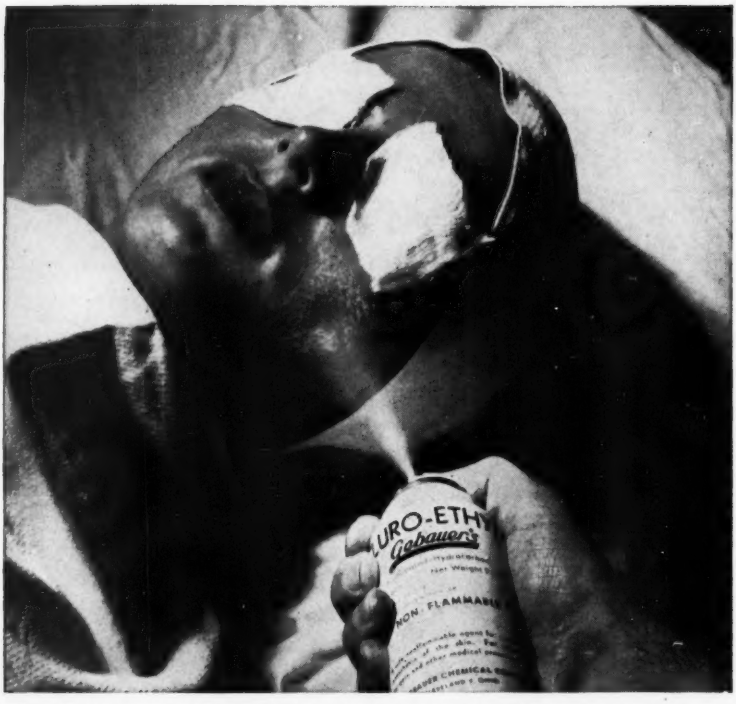

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base. Plastic squeeze
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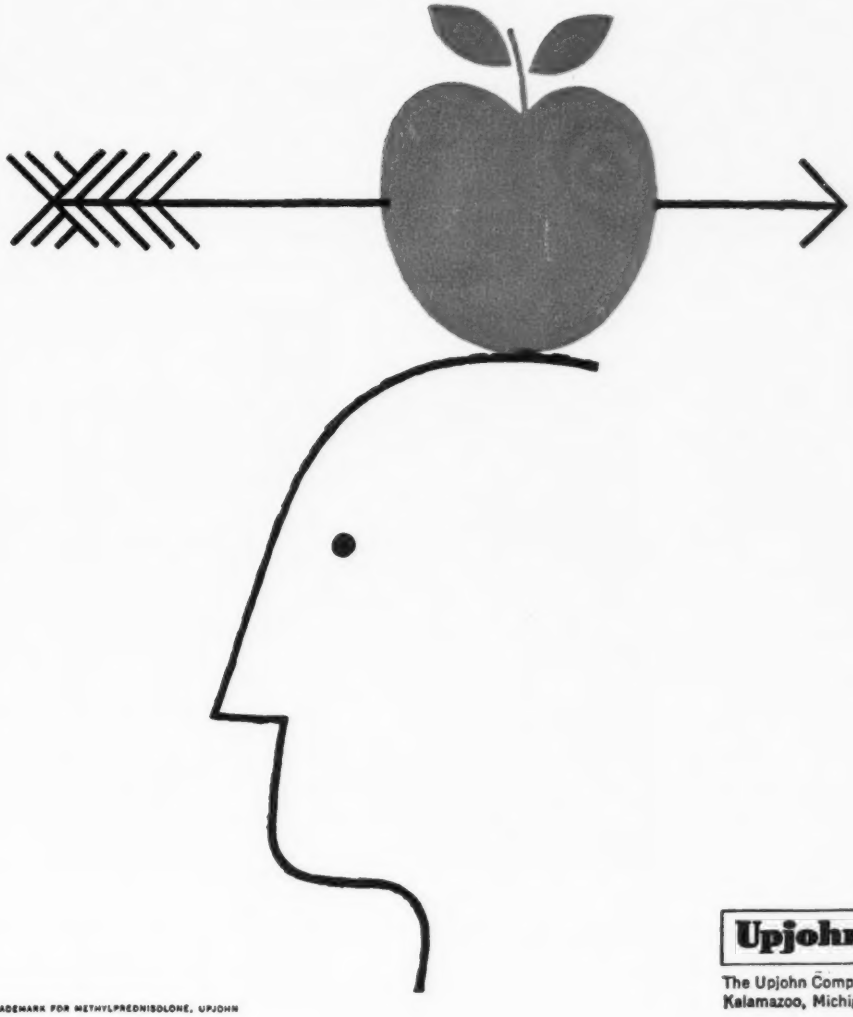

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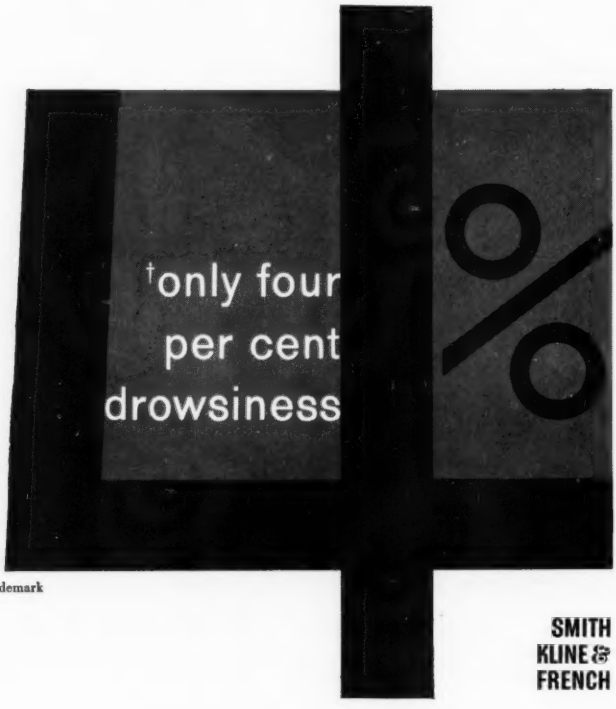

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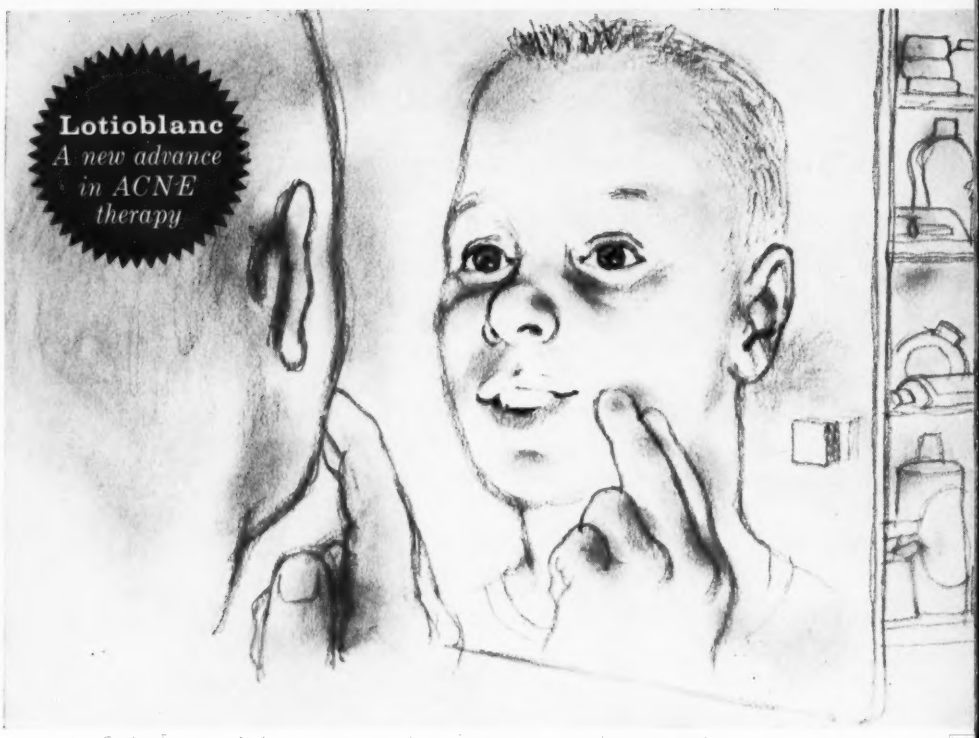

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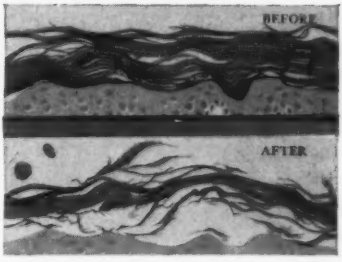

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REFERENCES: 1. Flesch, P.: Proceedings Scientific Session. Toilet Goods Assoc. June, 1958. 2. Samitz, M. H.: Ann. New York Acad. Sc. 73:1020, 1958. 3. Flesch, P., and Jackson Esoda, E. C.: Ann. New York Acad. Sc. 73:989, 1958. 4. Bleiberg, J., and Saltzman, J. A.: Clin. Med. 5:485, 1958. 5. Bleiberg, J.: Ann. New York Acad. Sc.: 73:1028, 1958. 6. Clyman, S. G.: Ann. New York Acad. Sc. 73:1032, 1958. 7. Welsh, A. L., and Ede, M.: Ohio M. J.: to be published.

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The Disease Called "Wildfire"

CLEMENT E. COUNTER, M.D., Los Angeles

The purpose of this paper is to describe some interesting features about the endemic pemphigus of central South America. This disease presents some special problems in classification, diagnosis, and therapy. Yet, in general, its care is somewhat similar to the care of serious dermatoses occurring in other parts of the world.

An application of hydrotherapy to the treatment of this endemic disease is described, and the results of this form of therapy are compared with other treatments also in use. My personal observations while in Brazil form the basis for most of the material used.

There is a legend in certain limited parts of central Brazil that some of the savages living there were able to transfer this strange disease to their enemies by blowing it on them. The Brazilian expression "fogo salvagem" literally means uncontrolled fire in much the same way that the word "wildfire" brings to mind a fire that has got out of control in the dry grass. Those who suffer from this disease truly experience a burning feeling that continues for days and months uncontrolled. Only when the patient is completely quiet does he get any degree of relief.

The usual patient is a young adult. Most patients are between 10 and 30 years of age [1,6] when the symptoms begin. Rarely, this disease may begin even earlier. Also, the onset may be later, in middle life. It may last 15 years or longer.

Typically, the first lesion is a vesicle on the central part of the face or on the upper part of the chest. Other vesicles and bullae soon develop over the face and scalp and upper trunk. Often lesions involve the whole trunk and the extremities and even the scalp. Mucous membrane surfaces lining the various orifices are not involved. As the bullous lesions become more numerous and extensive, an exfoliative dermatitis develops. In chronic cases when the bullous eruption extends onto the trunk, and while the disease is still in its early months, the exfoliation gradually becomes the characteristic lesion and the bullae are not so prominent.

Like other diseases characterized by extensive exfoliation, there is a distinct odor of dried serum. This odor is the distressing repulsive feature of fogo salvagem. The odor is persistent in a house where a patient with this disease has lived, even after thorough cleansing of walls and floors and complete interior painting.

Hypofunction of the various glands of internal secretion is common. The stature of one who has had this disease from childhood may be very short and puerile, even though he is more than 20 years old. Many are sterile sexually, even though their growth is not so retarded. Often the secondary sex characteristics are poorly developed. Patients of more than 20 years may have the stature and facial appearances of a child.

Submitted for publication April 18, 1959.

From the Department of Dermatology and Syphilology, The College of Medical Evangelists.

Fig. 1.—A 23-year-old woman with a four-month recurrence of "fogo salvagem." The previous attack was three years before. Note that the hands are spared.

The so-called dystrophic form of this disease has a process of decalcification of bones, leading to spontaneous fracture of the long bones. Such cases have extensive exfoliative dermatitis, more or less bullous eruption, and a lack of proper development of skeletal muscles, in addition to deficient calcification of the bones.

The various clinical variants of fogo salvagem are well classified by Vieira [5] as follows:

I. Acute type.
II. Subacute type.
III. Superacute type—terminates quickly in death.
IV. Chronic type.
1. "Frustre" (limited)—resembles pemphigus erythematosus (Senear-Usher).
2. Bullous exfoliative—commonest.
3. Pustular and ulcerative form.
4. Verrucous and papillomatous form.
5. Herpetiform form.
6. Hyperpigmented form.
7. Erythrodermic form.
8. Intensely foliaceous form.
9. Dystrophic form.

Hospital Matogrossense do Penfigo (Pemphigus hospital of Mato Grosso) is a small institution with a capacity of 55 patients. It is located about seven miles from the city of Campo Grande, in the state of Mato Grosso, Brazil. It attempts to admit only exfoliative pemphigus patients.

A group of 47 consecutive cases in this hospital were studied, and they were arranged according to types and forms of the Vieira classifications as follows: subacute, 2 cases; chronic, 43 cases, and ill-defined and unclassified, 2 cases. The 43 chronic cases were further classified as follows: bullous exfoliative form, 24 cases; intensively foliaceous form, 9 cases; pustular and ulcerative form, 5 cases; herpetiform, 2 cases; verrucous form, 2 cases, and hyperpigmented form, 1 case.

Costa [1] states that Brazilian endemic pemphigus resembles Cazenave's pemphigus foliaceous but that it differs from that disease in two outstanding respects: 1. Brazilian pemphigus is an endemic disease with geographic limitations restricting it to a more or less definite region. 2. The light case commonly referred to in Brazil as a forme fruste, or abortive case, closely re-

Fig. 2.—Lesions began on the face six months before; age 9 years.

Fig. 3.—Favorite posture, which is maintained night and day.

sembles pemphigus erythematosus (Senear-Usher).

The diagnosis of the forme fruste, or abortive type, is difficult. It requires a high index of suspicion and careful histological study to confirm. In general, the first vesicles begin on the face or upper back. This type may quickly become disseminated to include the whole body, or it may remain in these localized areas with slow clearing, thus becoming one of the abortive cases.

Brazilian pemphigus must also be distinguished from dermatitis herpetiformis, pemphigus vegetans, pemphigus vulgaris, lupus erythematosus, impetigo, eczema, seborrheic dermatitis, and exfoliative dermatitis.

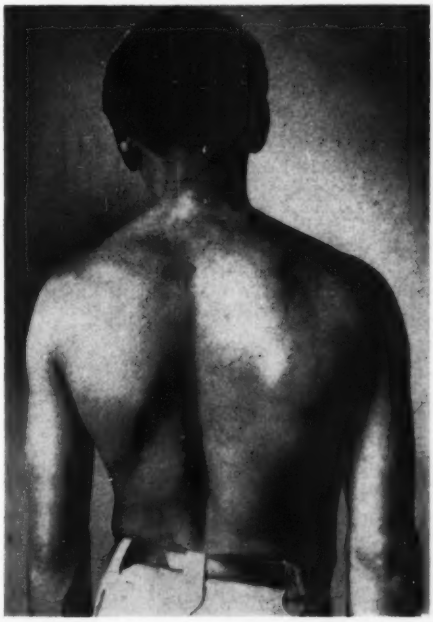
The microscopic study of a typical biopsy specimen shows alternating patches of hyperkeratosis and parakeratosis. Often squamous crusts are present which consist of parakeratotic layers between which are cellular elements including neutrophils and eosinophils and bacteria. The most important change is bulla formation. This takes place in the upper prickle-cell layer. The location of the vesicle or bulla in this disease is in the rete close to the granular layer, in contrast to the bulla formation in dermatitis herpetiformis, which is just under the epiderm. Vesicles and bullae of Brazilian endemic pemphigus also differ from pemphigus vulgaris and pemphigus vegetans, in which diseases the bullae form deep in the epiderm. Like Senear-Usher disease and Cazenave's pemphigus foliaceus, Brazilian endemic pemphigus typically forms bullae high in the epidermis just under the corneous layer.

A constant microscopic [1] finding is hyperpigmentation of the basal layer.

Another constant finding is a papillomatosis of the upper part of the cutis. Papillae are often slender and elongated and edematous and more or less infiltrated with wandering cells from the blood, including eosinophils. This produces grossly a verrucoid appearance of the skin.

Edema of the dermis often includes the hypodermis. It is also marked in the ex-

Fig. 4.—Scattered bullae and no scaling on the upper back of a young man; duration two months. This is an example of forme fruste, or abortive form, of the chronic type.



ternal sheath of the hair follicles. There is an atrophy of sebaceous glands in long-standing chronic cases.

The most outstanding need of these patients is good nursing because of the disabled condition of most of them. Yet even this is often denied them at home because of the distressing odor of dried serum that is always present, making them repulsive. This odor also emphasizes the fear among other members of the family and friends that the loathsome condition may be transferred to the attendant or other members of the family. This leads to an urge to have the patient taken elsewhere for care. There is such a lack of hospital facilities that the result is some kind of home care that often amounts to neglect. Often there is an attempt to "hide" the afflicted one. Patients are usually not very demanding. They are willing to sit in a folded up position not moving a muscle for hours. This goes on for days and months. The sufferer simply sits in an out-of-the-way place, where he is left undisturbed.

Estimates show that there are about 3,000 persons[6] in the central part of South America who have fogo salvagem. Only a small number are in hospitals. There are 250 in the Instituto Ademar de Barros in Sao Paulo in quarters admittedly designed for about 150. In Campo Grande there are 55 patients in a small facility designed for the care of not more than 30 patients. At least 100 other fogo salvagem patients are in the General Hospital in Bel Horizonte where they are not so distinctly segregated.

The number of cases that undergo spontaneous cure as determined by various means is about 19%.[4]

Ultraviolet-light treatments and vitamin therapy are used by doctors practicing in the region. Vitamin preparations are reasonably good. Some are given by mouth and others are injectable solutions. Many who later enter a hospital have had this type of therapy while they were yet ambulatory.

In the Instituto Admar de Barros in Mandaqui, Sao Paulo, much careful investigation of exfoliative pemphigus has been carried on for the last 20 years. Joao Paulo Vieira[5] wrote a report on pemphigus foliaceus in the *Archives of Dermatology and Syphilology* in 1940 and has written much on various phases of exfoliative pemphigus in Brazilian literature. More recently, Mario Fonzari,[2] in the same institution, has given us the results of orally administered quinacrine (Atabrine) hydrochloride. It is evident by visiting Dr. Fonzari that he believes this medication is even more efficacious than is indicated by the statistical study of 151 cases which he reports. These studies show significant trends in therapeutic results. Of 151 cases treated with quinacrine, 58% (87 cases) went into regression. Some of these required only four months, with a total dosage of 50 gm. of quinacrine. Others of the recovered 87 cases required as long as two years and a total of 800 gm. of the medication. Of the 151 cases treated with quinacrine, 17 showed some toxicity for the drug. None of these was serious. All signs of toxicity disappeared promptly upon withdrawal of the medication.

Another entirely different approach to the treatment of the disease known as "wildfire" was originated deep in the endemic area near Campo Grande, Mato Grosso.[3] It is composed chiefly of local therapy, yet the nutritional support of the patient receives careful attention. The procedures given below become a unit which are repeated two to three times a week:

1. The patient is given a steam bath followed by a soap-and-water washing to remove scales.

2. He is then placed in a lukewarm bath containing an infusion of green Eucalyptus leaves. He is blotted and fanned dry.

3. A black tar containing liquid the consistency of paint is applied to the whole body with a small paint brush. The hair is cut short so that the black liquid can be applied to the scalp as well as to all other parts of the skin.

4. All patients are given a quinine and iron tonic orally daily.

The black liquid is called "Jamarsan" in respect to its originator, Isadore Jamar, now dead. Its ingredients are as follows:

	Gm.
Sulfur ppt.	150
Zinc oxide pwd.	120
Boric acid pwd.	100
Calcium hydroxide (lime)	100
Turpentine	15
"Industrial pixe" (coal tar)	3,000
Cottonseed or peanut oil	1,500

The man, Jamar, was a layman who had had seven years of the eight-year medical course of a medical school in the Argentine. He became active politically and one day found himself on the wrong side. To escape apprehension he took the way up the Rio Paraguay. Eventually, he came into the southern part of Mato Grosso, Brazil, about 50 miles west of Campo Grande. There he married and lived among the poor of that section. He subsisted on the small fees he could get by a practice of medicine, such as could be expected of a medical student. He was hiding.

The use of tar must have been suggested by some of his dermatological training while he was yet in the Argentine. He said that his first "patient" was a cat which was so covered with a dermatitis that it had lost all of its hair. The cat recovered, and he treated another. Later he treated a dog, and later after he had reached Mato Grosso he became courageous enough to use a mixture of tar, oil, and sulfur on a human who suffered from "wildfire." The patient did well. After that many were treated by Jamar. He claimed that during his life he had "cured" 40 people of fogo salvagem.

This treatment is vigorous. Good use of it requires that cases be selected who are sufficiently strong to tolerate it. In this connection it is recalled that persons who have fogo salvagem are older children and young adults. Unless their treatment is long delayed to a time when invalidism has severely weakened them, they are rather uniformly strong enough to be treated by this method.

Its immediate benefits are to relieve the tormenting, burning and itching distress. This is produced after the first treatment with baths and tar. The second and scarcely less important benefit is the deodorizing effect. The hospital near Campo Grande has no odor such as is common to hospitals where exfoliative dermatoses are treated. Especially does it lack the intense odor of the sick room where a patient who has exfoliative pemphigus is being treated. There is only a faint odor of tar. A third benefit, which may be the most important, is the hyperpigmentation that develops as a result of baths and tar-compound applications.

Experience with this type of hydrotherapy and local application of coal-tar compound in Hospital Matogrossense do Penfigo shows encouraging improvement and cure rate. One hundred eight patients with exfoliative pemphigus were treated in 1957. Forty-eight were patients who had entered in 1956 and whose treatment was continued into 1957. Sixty new pemphigus patients entered during 1957. Of these 108 patients, 42 (38.88%) were continued under treatment into 1958. Sixty-six patients were discharged during 1957. Thirty-four (31.48%) were discharged as totally arrested. Nineteen (17.58%) were discharged with improvement estimated at more than 80%. This group chose to continue some form of modified treatment at home rather than stay in the hospital longer for the treatment of residual lesions. Nine (8.34%) chronic patients were transferred home as having had adequate experience with hospital care to demonstrate no further improvement. Four (3.44%) died in the hospital. During the year six former patients returned. They had received previous treatment in the hospital and had been discharged as totally arrested but had recurrences.

During their stay in the hospital patients receive other treatment than baths and tar compound applications as are indicated from day to day. Antibiotic injections of streptomycin and penicillin are used to control intercurrent infections. A vitamin combina-

tion is often used as an injection. Some chloroquine (Aralen) was used, and some protoxalate of iron was given. A type of crude coal-tar ointment, somewhat milder than Jamarsan, is used on residual lesions such as may remain on the face and neck and more tender parts of the body.

Report of a Case

The following report gives an example of this treatment applied to a Brazilian woman as home therapy. The patient was a white married woman, aged 32, who had no children. During February, 1952, she began to have bullae on her nose and cheeks. Within two weeks this eruption extended to include every part of her body. Bullae and vesicles were widely distributed over her face, trunk, and extremities, and there were also plaques of greasy scales between the bullous lesions. There were no lesions on the mucous membranes. From the first months she was aware of an increase of symptoms during the week preceding menstruation and an improvement during the time of menstruation. This continued even after her improvement during treatment.

At first treatment was chiefly vitamin pills and injections from private physicians in the city of Sao Paulo. She was given much cortisone therapy also. Her husband sold their home and his truck, which he had used in his business, to obtain about $20,000. This was all spent on medicines, especially cortisone, and on hospital costs during the 18 months following February, 1952.

She was hospitalized in a public hospital for the treatment of pemphigus four times amounting to a total of five months. Each time the diagnosis was exfoliative pemphigus. General discouragement because of confinement in the hospital caused her to leave each time after about five weeks.

In August, 1953, she was examined by Dr. L., in Sao Paulo. She appeared well nourished, having only mild evidence of former pemphigus lesions on the upper back and on the chest. These remnant lesions were mottled pink to brown in color. Her face was round, and her abdomen and hips were large from retained fluids—the side-effects of the cortisone therapy. As soon as cortisone was discontinued, much eczematous scaling appeared and scattered bullae developed on the trunk and extremities. There was much more exfoliation and exudation than bullae formation. According to the Vieira classification, she had a bullous exfoliative form of chronic Brazilian pemphigus.

Treatment was begun with a soap-and-water bath. All vesicles and scales were removed with a small soft nail brush. After this a neutral bath in a mild infusion of Eucalyptus leaves was given. When her body was thoroughly dry, Jamarsan was applied to the entire body with a small paint brush. Cotton was used as an applicator of the black preparation to the face. An injectable Ciba preparation called "Cibalena" was given to relieve pain. The action of this medication resembles that of acetylsalicylic acid (aspirin). She had some nausea and vomiting after five hours. This distress of vomiting was relieved by injections of a mixture containing inositol, choline, and liver extract.

This whole procedure was repeated every 48 hours. This was carried on for two months. After three weeks she was much improved. Only remnant lesions remained on her back and on the sides of her trunk. All baths and Jamarsan applications were done at home.

Her appetite was somewhat reduced in general in addition to the nausea episode which followed each Jamarsan application. There was no need for laxatives. There were headaches but no urinary complaints. The urine did not show unusual findings.

A vegetarian diet was considered an important supportive measure both during the active treatment and during the months that have followed. Protein was furnished in sufficient amount from eggs, milk, and cheese, as well as from lentils, beans, and two kinds of nuts—cashews and Brazil nuts. No coffee nor alcoholic beverages were allowed.

This patient has remained well since November, 1953, when her active treatments were discontinued. She received 12 weekly Russian (steam) baths following the tar-mixture applications. These hydrotherapy treatments seemed to help in clearing the dark pigmentation which developed during the time of tar treatments. The patient is happy. She can do her housework and once again mingle freely socially.

Comment

Much more chemical research is needed to explain the action. So far, various attempts to modify the original formula made by Isadore Jamar, to make it more refined and smooth, and not so vigorous, have resulted only in taking from it the healing effects for exfoliative pemphigus.

Perhaps the production of greater light tolerance by the patient is the one effect common to the types of treatment which have been shown to increase the spontaneous cure rate. At Instituto Admar de Barros, quinocrine has significantly improved the low spontaneous-cure rate. Quinocrine

is known to produce improvement in diseases showing intolerance to sunlight, such as chronic discoid lupus erythematosus and polymorphic light-sensitive eruption.

In Hospital Matogrossense do Penfigo an increase in the spontaneous cure rate has been accomplished with another method which employs hydrotherapy and a coal-tar-containing mixture applied locally repeatedly. One of the early effects of this treatment is the production of hyperpigmentation and the frequent production of papillomas which may be evidence of increased tolerance to light. Vieira[5] states from his earlier observations that the forms (of fogo salvagem) which show most tendency to regress spontaneously are the hyperpigmented form and the verrucous form.

Hyperpigmentation continues to be observed as a favorable sign for regression of the disease. It was pointed out among patients seen in the hospital in Sao Paulo. Patients in the small hospital near Campo Grande were very much aware of any developing papilloma. Each patient readily and cheerfully pointed out his "wart" if he had one. All patients at Campo Grande under the so-called Jamarsan treatment were more or less hyperpigmented.

Conclusion

A disease closely resembling exfoliative pemphigus is described. It is endemic and limited geographically to parts of southwestern Brazil and to the adjoining parts of other countries.

Treatment of this odd disease is discussed. Quinacrine hydrochloride by mouth produced regressions in 58% of 151 patients treated in Sao Paulo.

An entirely different type of therapy practiced deep in the hinterland of Mato Grosso consists chiefly of hydrotherapy followed by the application of a tar preparation. Repeated three times a week, it brings about a rather permanent arrest of the disease. At least 56.5% of the patients treated with the tar preparation are arrested or improved sufficiently to have home therapy that finishes their complete arrest of pemphigus. Patients seem to value the relief from itching and from the odor even more than the cure possibilities.

Details of the treatment with tar are given. Actually, it is an application of hydrotherapy to the treatment of this endemic type of pemphigus.

It may be that the chief value of "tar treatment" for patients with Brazilian type of pemphigus foliaceus is its ability to produce hyperpigmentation.

1720 Brooklyn Ave. (33).

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Extramammary Paget's Disease with Metastasis to Lymph Nodes

Report of a Case

PHILIP H. PROSE, M.D., and ARTHUR B. HYMAN, M.D., New York

Sweat gland carcinomas which manifest themselves in overlying skin as extramammary Paget's disease and also metastasize to organs other than skin are rare.[12,13] Knowledge regarding the clinical features, behavior, and response to therapy of these neoplasms is based on few cases. It is the purpose of this presentation to report such a case and to make available more information concerning these tumors.

Report of a Case

A white man, 82 years old, was admitted to the clinic on July 30, 1957, with a lesion of the skin of the left groin of 14 years' duration, which had slowly increased in size to involve the skin of the superomedial aspect of the left thigh, the left side of the scrotum, and the left lower quadrant of the abdomen. For six months prior to his visit to the clinic, he had noted swelling of the left foot. Hemorrhoidectomy and an excision of a fistula *in ano* had been performed in 1945; he recalled no other operation or illness.

The patient was well nourished and appeared younger than his stated age. The skin in the left inguinal fold and on the adjacent thigh, abdomen, and scrotum was denuded, and the surface was dusky red, granular, and fissured and was covered by mucopurulent, foul-smelling exudate. The lesion was irregular in contour and was for the most part well demarcated. It measured 10×10 cm., and it was elevated 0.25 cm. above the adjacent healthy skin surface (Fig. 1). The left foot was edematous.

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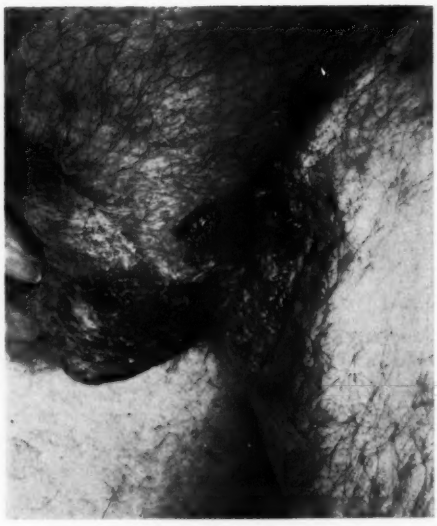

Fig. 1.—The left inguinal area and left side of scrotum shows a well demarcated tumor with a granular surface covered by mucopurulent exudate.

Following the histologic examination of two 5 mm. biopsy specimens taken from one edge of the lesion (see pathologic findings), the involved area was treated with x-rays (100 kv., 10 ma., HVL 0.9 mm. Al, 25 cm. TSD, 226 r per minute), 680 r on each of five visits between Feb. 19 and March 5, 1957, for a total of 3,400 r. The irradiated lesion gradually epithelialized except for a 5.0×1.0 cm. superficially ulcerated area with a slightly raised and indurated border, on the left side of the scrotum.

The patient was hospitalized on Nov. 8, 1957, because the edema, first noted to involve the left foot, had slowly progressed to involve the left lower extremity, penis, scrotum, and left buttock. On Dec. 20, 1958, the left inguinal region was surgically explored and two lymph nodes were removed for study. The patient was discharged from the hospital on Jan. 3, 1958.

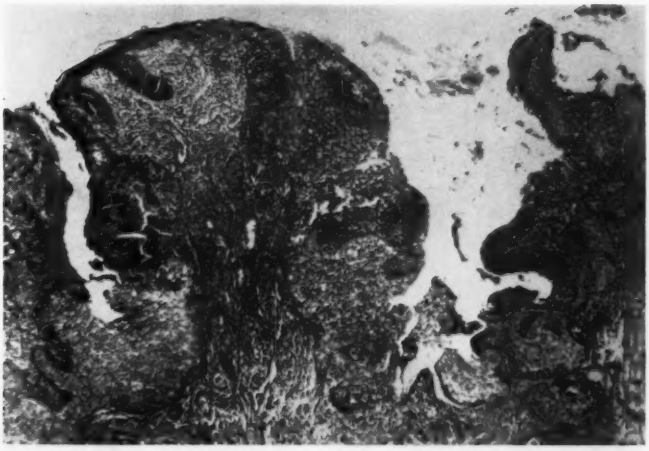

Fig. 2.—The epidermis with deep folds shows aggregates of pale-staining tumor cells in the folds. Hematoxylin and eosin; reduced 40% from mag. × 75.

The results of several complete blood cell counts and urinalyses were within normal limits. The erythrocyte sedimentation rate and the amounts of blood urea nitrogen and glucose, plasma potassium, serum acid and alkaline phosphatase, and serum sodium were within normal limits. Total plasma proteins were 8.3 gm. per 100 cc.; the albumin-globulin ratio was 1.08:1.0. The results of serologic tests for syphilis (Mazzini, VDRL, and Wassermann reactions) were negative. Radiographic examination of the chest, colon, and terminal ileum, pelvis, lumbosacral spine, and femora showed no abnormalities. An intravenous pyelogram showed prompt excretion of dye and spreading of the inferior and middle calyces on the left side; the abnormal filling of these calyces suggested an intrarenal mass, probably a cyst. On proctoscopic examination there was no gross abnormality.

Pathologic Findings

Histologic examination of the biopsy specimens from one edge of the lesion showed the epidermis thrown into folds, with the subjacent basement membrane intact throughout (Figs. 2 and 3). In some areas the epidermis was normal in thickness or moderately acanthotic. Among the normal-appearing glycogen-free cells of the stratum spinosum, but not connected to them by intercellular

Fig. 3.—The epidermis with deep folds shows greatest concentration of mucin-producing cells in the folds and fewest in the superficial epidermis between the folds. Black dots represent blue-green material within the cytoplasm of cells. Alcian blue-periodic acid Schiff; reduced 30% from mag. × 75.

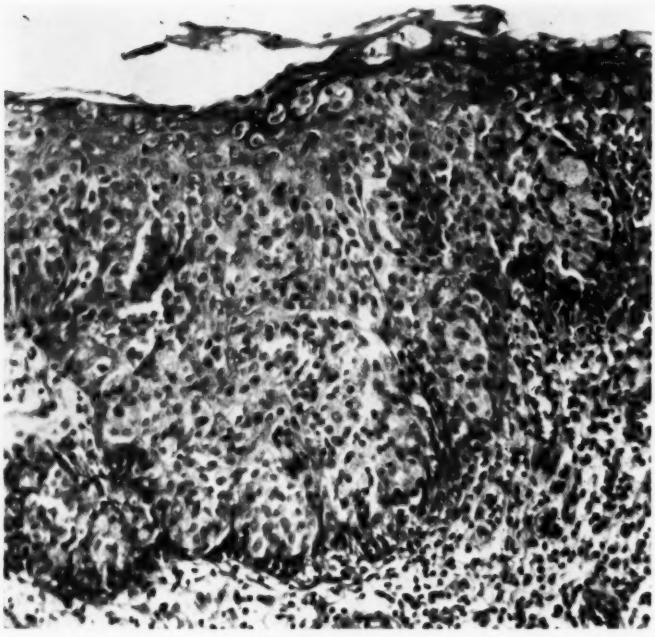

Fig. 4.—The moderately acanthotic epidermis is disorganized by isolated and clumped tumor cells; the latter are also seen in the keratin layer. Hematoxylin and eosin; reduced about 15% from mag. × 280.

bridges, there were isolated, as well as clumps of large rounded cells. These latter had centrally placed round or spindle-shaped nuclei with a fine chromatin network, and the nuclei were surrounded by a moderate amount of clear basophilic cytoplasm with well-defined margins. Hyperchromatic nuclei and nuclei so disposed as to give the cells a signet ring appearance were sometimes seen. Some of these rounded cells were found in the overlying keratin layer (Fig. 4). The clear basophilic cytoplasm was stained orange-red by the mucicarmine stain and blue-green by the Alcian blue technique.

In other areas the epidermis was thick and formed deep folds. Here the basal cells were cuboidal, though absent in some parts. The Malpighian cells were for the larger part not identifiable because they were replaced by aggregates of two types of cells. In some aggregates there was a mixture of the two types, but in most the cell type tended to be uniform. (*a*) One type of cell was round or oval, containing

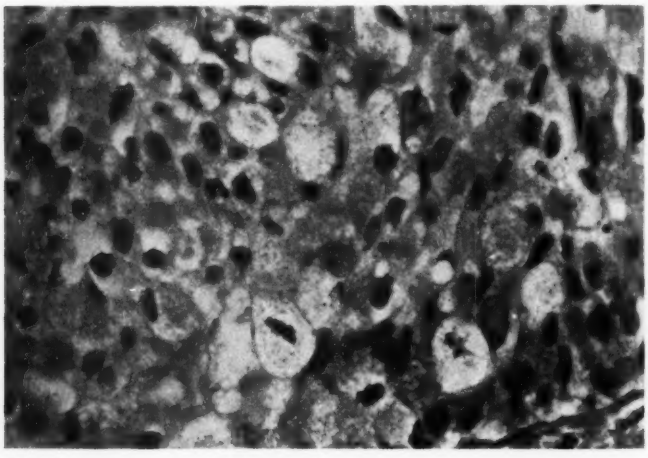

Fig. 5.—A portion of epidermis showing large round cells with hyperchromatic nuclei surrounded by reticulated cytoplasm, mitotic figures in the lower part of the photograph, and occasional "signet-ring" cells. Hematoxylin and eosin; reduced 40% from mag. × 825.

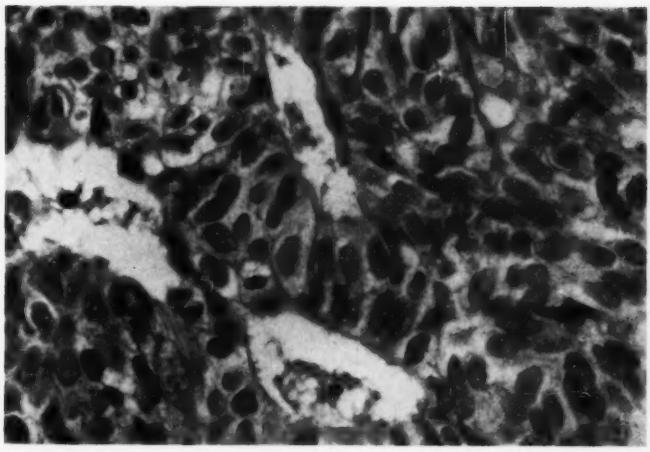

Fig. 6.—A group of columnar cells arranged about spaces in acinar pattern seen within epidermis. Hematoxylin and eosin; reduced 40% from mag. × 900.

an irregularly shaped, hyperchromatic nucleus surrounded by a large amount of reticulated basophilic cytoplasm with distinct outlines (Fig. 5). The cytoplasm of these cells also took the mucicarmine and Alcian blue stains. These cells were most numerous in the depths of the folds, somewhat less numerous along the sides of the folds, and fewest in the surface epithelium between the folds where the concentration of the tumor cells decreased as the distance from the

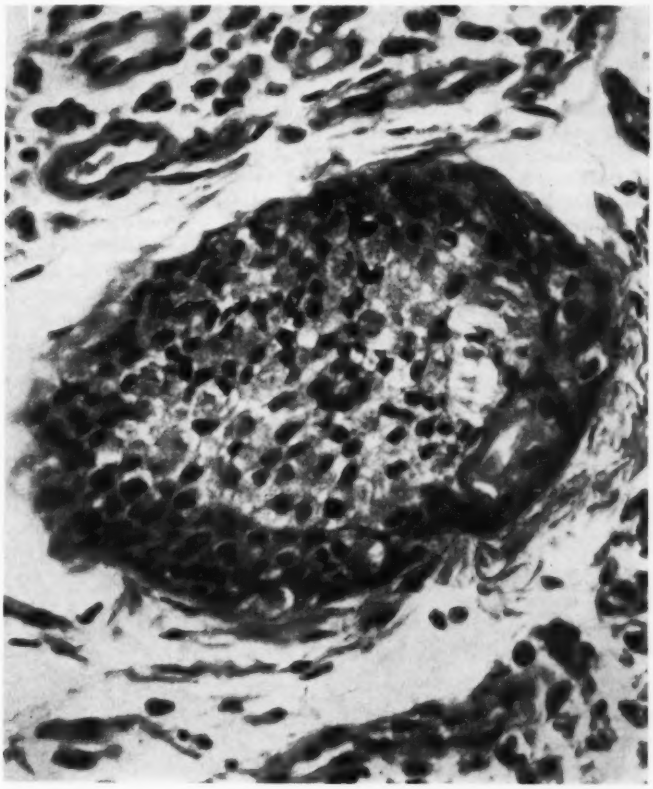

Fig. 7.—A sweat duct shows the wall expanded and largely replaced by tumor cells, the lumen of the duct surrounded by the cuticle in the right side of the wall, an intact basement membrane, and plasma cells in the infiltrate. Hematoxylin and eosin; reduced 10% from mag. × 750.

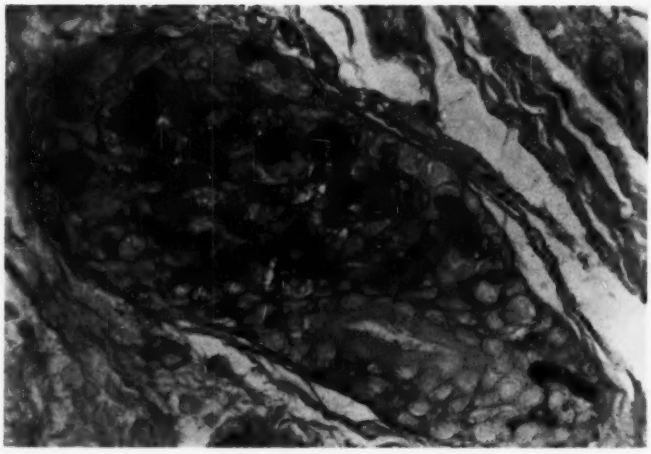

Fig. 8.—An oblique section of an enlarged sweat duct with slit-like lumen surrounded in part by mucin-producing tumor cells. Alcian blue-periodic acid Schiff; reduced 40% from mag. × 700.

folds increased (Fig. 3). (*b*) The other type of cell was columnar or spindle-shaped, containing an oval nucleus with a fine reticulated chromatin network and one or two small nucleoli, surrounded by a moderate amount of pale eosinophilic cytoplasm with indistinct outlines. Large amounts of glycogen were noted within the cytoplasm. Mitotic figures were infrequently seen. Within the areas composed of this type of cells an acinar pattern was suggested by irregularly shaped clefts and round and oval spaces, about which the cells tended to be grouped in palisade arrangement (Fig. 6). These spaces contained eosinophilic material, which was stained, to some extent, orange-red by the mucicarmine and blue-green by the Alcian blue; the surrounding cells were rarely stained by these techniques. Within the cutis, occasional sweat ducts showed areas in which their walls were expanded by the previously described abnormal cells with vacuolated or clear basophilic cytoplasm; the outer basement membrane and the inner cuticle were intact (Figs. 7 and 8). Iron was not demonstrable in these ducts by the Prussian blue Gomori technique. The capillaries in the cutis were dilated and congested, lined by swollen endothelial cells, and surrounded by a dense infiltrate of plasma cells with an occasional lymphocyte and polymorphonuclear leucocyte.

Frozen sections of one of the specimens of the skin were stained with Sudan IV but failed to show any sudanophilic material.

One of the excised lymph nodes measures 2.5×2.0×0.8 cm.; the other, 1.0×0.8×0.5 cm. The nodes were purple-red, firm, and encapsulated. The

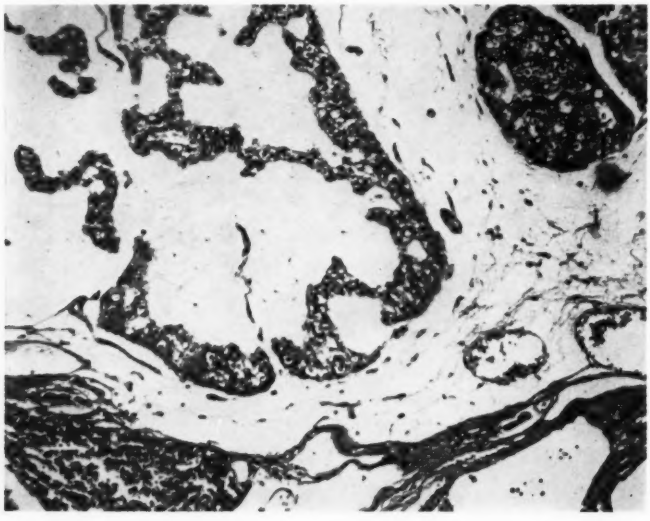

Fig. 9.—A portion of lymph node, largely replaced by mucin within which strands and aggregates of tumor cells are seen with a group of lymphocytes in the lower left corner. Hematoxylin and eosin; reduced 10% from mag. × 100.

cut surface was uniform in appearance, gray, and glistening. Histologic sections of the nodes showed occasional focal collections of lymphocytes, but the normal architecture was almost completely replaced by an eosinophilic, homogeneous, ground-glass-like material which was mucicarminophilic. Within this mucin there were various-sized clumps and strands of small, round, or cuboidal cells, occasionally forming acini (Fig. 9). The cells contained centrally placed nuclei with a delicate chromatin network, surrounded by a small or moderate amount of eosinophilic granular cytoplasm with distinct outlines. These cells were rarely mucicarminophilic.

Comment

The diagnosis of Paget's disease in sites other than the nipple was first suggested as a possibility by Sir James Paget [8] in the original report describing the disease. He cited a patient with persistent rawness of the glans penis for more than one year, who developed carcinoma in the substance of the glans. The first clear-cut case was reported by Radcliffe Crocker [2] in 1889. The patient, a man, aged 60, had a persistent lesion of the scrotal, penile, and pubic skin. Histologic sections of the lesion showed "Paget" cells in the epidermis, a subjacent alveolar carcinoma, and "conversion of the sweat cords and ducts with cancerous structures."

Until investigators presented convincing evidence for the now widely accepted opinion that Paget's disease of the breast is always associated with an underlying carcinoma of the mammary ducts there was much confusion regarding the nature of the pathologic process in this disease. A parallelism exists in this respect between Paget's disease of the breast and extramammary Paget's disease, since some claim that the extramammary lesion originates in the underlying sweat apparatus and then secondarily involves the skin [5,14]; others claim that the disease may first arise in the skin or may develop simultaneously in the skin and underlying sweat apparatus. The suggestion that the tumor cells originate in the epidermis is based on the presence of large numbers of tumor cells in the epidermis in the apparent absence of carcinoma in the subjacent corium.[6] In order to prove this, one would have to excise a lesion in its entirety and examine serial histologic sections, because only search through many sections in different blocks of tissue from the same tumor in a case studied by Dockerty and Pratt [3] showed the presence of carcinoma in the corium.

The concept of extramammary Paget's disease has been beset by a further problem. Some investigators accept only those cases in which the skin manifestations are associated with a subjacent sweat gland carcinoma.[14] Others are satisfied with less restrictive criteria, i. e., the finding of "Paget" or cancer cells within an otherwise healthy or at least non-neoplastic epidermis, and, of somewhat lesser importance, the presence of the clinical features of Paget's disease. With such criteria one could class as extramammary Paget's disease cases of carcinoma of the rectum with secondarily involved skin, certain melanomas, and cases of carcinoma implanted into skin.

In view of the findings in the case here presented, the discussion will be limited to extramammary Paget's disease associated with sweat gland carcinoma.

There are some 30 reported cases of extramammary Paget's disease [4,5,14]; in most there were no evident metastasis. Women were affected twice as often as men. The anogenital region was the site most frequently involved; in all but one of the remaining cases the axilla was the site of the disease; and in one case the glands of Moll in the eyelid were involved. Most of the patients were in the sixth decade. The disease, as in the case here reported, was usually of long standing, the majority of patients having had the lesion for six years or longer at the time of treatment.

There are seven reported cases of extramammary Paget's disease that had metastasized to sites other than skin.[1,3-5,11,14,15] In common with the case here described the skin of the anogenital region or the axillae was the site of involvement, an adenocarcinoma was found in the subjacent

corium, and the clinical appearance of the skin lesion usually preceded the observation of metastasis by many years. In the case here reported there was an intraductal carcinoma of the sweat glands similar to that noted in the mammary ducts in Paget's disease of nipple. The outer basement membrane and inner cuticle of the ducts were everywhere intact, and an infiltrating carcinoma was not seen in the sections examined; however, in view of the limited amount of tissue for examination, the existence of an infiltrating carcinoma within the gross lesion cannot be excluded. The much greater concentration of tumor cells within the epidermal folds as compared with the intervening superficial epidermis was thought to be due to invasion by tumor cells from the epidermal folds into the superficial epidermis. The folds may have represented bizarre sweat ducts or hair follicles, or they may have been the result of the sheer massive concentration of tumor cells. The similarity of the findings in this case and those in Paget's disease of the nipple would suggest that the skin was invaded by the malignant cells originating in the sweat apparatus, rather than the reverse. However, one cannot exclude the possibility that the tumor cells had a simultaneous origin in the sweat ducts and the epidermis. Although most of the reported cases of extramammary Paget's disease appear to have an apocrine gland origin, it is not possible to conclude in this case whether the involved sweat ducts were of the apocrine or eccrine type. While sections of the sweat ducts did not contain iron when stained by the Prussian blue technique of Gomori, this does not establish the apocrine or eccrine nature of the involved glands since some apocrine as well as the eccrine glands react in a similar manner. Moreover, both types of sweat glands are found in the genital region as well as the axillae. It cannot be arbitrarily concluded that the tumor arose in apocrine glands, because Parsons and Lohlein[9] reported that the adenocarcinoma in the corium of a case of Paget's disease of the groin and scrotum could have begun in the eccrine glands and the photomicrographs illustrating their report are entirely compatible with this impression. Nevertheless, the difficulties in differentiating between the two types of sweat glands particularly when they are not in their characteristic stage of secretion must be borne in mind.

The absence of pilosebaceous structures in the section examined from the lesion here described may have been the result of long-standing inflammation. Rolleston and Hunt,[10] in 1897, reported that sebaceous glands were absent in histologic sections of a case of extramammary Paget's disease; though they attributed the origin of the tumor to the sebaceous glands despite their observation of "large vacuolated squamous epithelial cells" within the sweat ducts.

Mucin production by the cells of the tumor was a striking feature in the case here reported. In all cases of extramammary Paget's disease of the anogenital region studied by Helwig[6] some of the cells contained mucin. He attributed this finding to the fact that part of the skin in this region is of endodermal origin. However, this does not explain the presence of mucin in tumor cells in extramammary Paget's disease of the axilla, in metastasizing sweat gland carcinomas that are neither associated with extramammary Paget's disease nor located in the anogenital region, and in benign sweat gland tumors. Another explanation for mucin production by sweat gland tumors may be found in some physicochemical disturbance within the tumor cells.

In the case here presented, mucin was only rarely observed within the tumor cells in the lymph nodes. These cells were situated in pools of mucin, but at a distance from their blood supply, and, therefore, had probably lost their capacity to produce mucin.

Keasbey and Hadley[7] suggested that the occurrence of mucin within clear-cell hidradenomas was of prognostic significance, since it was only found in four cases, three of which were histologically atypical

and one case in which the tumor metastasized.

Plasma cells are the preponderant inflammatory cells in the cutis in extramammary Paget's disease. This type of infiltrate is occasionally considerable in sweat gland carcinomas in which the skin surface is not involved.

In addition to the seven reported cases of metastasizing sweat gland carcinoma that showed the clinical and histological features of extramammary Paget's disease, there are 23 acceptable reported cases of sweat gland carcinomas that metastasized but did not show these features.[12,13] Most were papillary cyst-adenocarcinomas which developed as nodules in the skin, clinically suggestive of dermatofibrosarcoma, keloid, metastatic carcinoma, lymphosarcoma, or lipoma, and after many years metastasis became clinically evident and was usually first noticed in the regional lymph nodes. About one-third of these tumors were found in the anogenital or axillary regions, one-fourth in the region of the scalp, and the others about the wrist and foot. There are reports of a papillary cystadenoma of the wrist and of hidradenoma of the vulva which were histologically apparently benign, but metastasized to regional lymph nodes.

Although the lesion here reported improved in appearance with roentgen therapy, a small ulcer of the skin persisted. One may assume that the lesion had already metastasized at the time of the patient's first visit to the clinic, in view of the edema of the left foot, which subsequently involved the entire lower extremity. The failure of radiation in the treatment of extramammary Paget's disease, and sweat gland carcinomas in general, has been recorded by others.[1,4,7] Although Fisher and Beyer[5] considered that radiotherapy was ineffective in their case of extramammary Paget's disease with widespread metastasis, the primary lesion was controlled by x-rays, since a careful autopsy of their patient failed to show any residual tumor in the irradiated perianal skin.

Desiccation, electrical, or chemical cauterization, etc., on the assumption that the lesion arises in the epidermis and does not necessarily involve the corium, is, in the light of our present knowledge, perhaps as unwise as treating Paget's disease of the nipple by similar techniques.

Excision of the lesion with wide margins of surrounding healthy skin and subcutaneous tissue is the treatment of choice, though recurrences have often been reported following this mode of therapy.[3,4] Similarly, sweat gland carcinomas which are not associated with extramammary Paget's disease tend to recur after local excision.[12] Sekiguchi[11] noted in his patient with extramammary Paget's disease of the scrotum that the penile skin in contact with the scrotal lesion showed two small carcinomatous ulcers, probably the result of tumor implants. The tumor may also perhaps arise in multicentric foci, and thus its eradication is made more difficult.

Since "ectopic" apocrine glands (as well as eccrine glands and sweat gland carcinomas) may be found in many areas of the skin, the development of extramammary Paget's disease in sites other than those already reported, i. e., the anogenital region and the axillae, would appear to be a possibility. The apocrine glands with their surrounding stroma, somewhat like the breast in females, are influenced by endocrine secretions; these glands begin to function at puberty and may show cystic changes at the menopause. It is of interest in this regard that the reported cases of extramammary Paget's disease have occurred at the cephalad and caudad extremities of the embryologic milk line. Apocrine sweat glands are present in substantial numbers in the sites in which extramammary Paget's disease has already been described, and this probably explains the occurrence of the disease in the anogenital region and the axillae. But, additional factors may be in operation in these areas; pH of the skin surface is high as compared with most other areas; friction and maceration of the skin are not uncommon.

Early recognition of cases of extramammary Paget's disease and sweat gland carcinomas in general is essential if better therapeutic results are to be obtained. In the differential diagnosis of a weeping lesion of the anogenital region or axilla, and of a nodular lesion in the anogenital region, axilla, or scalp, a sweat gland carcinoma should be entertained. The possibility that this disease may occur in other locations should be considered.

Summary

An 82-year-old man who had Paget's disease of the groin for 14 years developed edema of the ipsilateral lower extremity. Histologic examination of the diseased skin and regional lymph nodes showed a mucin-producing sweat gland carcinoma. The histologic findings in this tumor are presented. The pathogenesis and therapy of this disease are discussed.

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Use of Relaxin in Management of Ulceration and Gangrene Due to Collagen Disease

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Relaxin * was discovered by Hishaw,[1] in 1926. He noted that injection of the serum of pregnant rabbits into virgin guinea pigs produced relaxation of the pubic symphysis.

The use of relaxin in the treatment of scleroderma was proposed by Casten and Boucek.[2] They stressed its advantages in the management of the disabling peripheral vascular symptoms, which are such a distressing feature of the systemic form of the disease.

On the basis of their report we used relaxin in the treatment of two patients who presented with severe Raynaud's phenomenon and who had associated trophic ulceration and gangrene.

Report of Cases

CASE 1.—A housewife, aged 57 years, was admitted to the Henry Ford Hospital on July 17, 1957. Her chief complaints were as follows:

1. Raynaud's phenomenon of three years' duration;
2. Weakness, becoming progressively worse during the preceding six months and affecting primarily the arms and thighs;
3. Occasional muscle pain, not severe or constant, and involving especially the forearms, arms, shoulder girdle, and thighs;
4. Pain, severe and unremitting, preventing sleep, of three months' duration, and located in the fingers;
5. Ulceration of the tip of the middle finger, left hand, of five months' duration;
6. A tense fusiform swelling of the right index finger, with ulceration of the palmar aspect of the terminal phalanx, and gangrenous changes at the tip.

Submitted for publication Feb. 14, 1959.

From the Department of Dermatology, Henry Ford Hospital (Clarence S. Livingood M.D., Chairman).

* The relaxin used in this study was supplied as Releasin by the Warner-Chilcott Laboratories, Morris Plains, N. J.

The pertinent physical findings on admission were as follows: a 57-year-old white woman in severe pain, who showed a heliotrope tinge in the periorbital region with periorbital edema, an overall reddish-purple cast to the face and upper anterior chest, due to multiple telangiectasiae, and a brownish hyperpigmentation of the abdomen.

The tips of all the fingers were red, shiny, and atrophic. There was a shallow ulceration of the tip of the middle finger of the left hand. There was a fusiform swelling of the right index finger, and the overlying skin was tense, red, and shiny. The tip of this finger was black and gangrenous without any clear line of demarcation. The peripheral pulses were palpable and strong.

Her intolerance to cold was so severe that she would develop very severe pain after being in an air-conditioned room for only a few minutes.

Our initial impression was that she had a diffuse collagen disease, probably best classified as scleroderma—dermatomyositis with Raynaud's phenomenon. Exhaustive laboratory investigation, x-ray studies, and biopsies were performed. The only significant laboratory finding was the presence of cryoglobulins. X-ray studies of the gastrointestinal tract were suggestive, but not diagnostic, of sclerodermatous changes in the esophagus and stomach. X-rays of the hands showed osteoporosis, soft tissue calcification, and "tufting" of the terminal phalanges. Biopsy specimens of skin and muscle, from the deltoid region, showed no evidence of scleroderma or dermatomyositis. A thorough search revealed no associated malignancy. There was no evidence of primary vascular disease.

On July 7, 1957, the patient was started on Releasin (brand of relaxin), 1 cc. intramuscularly per day. Each cubic centimeter of Releasin contains the equivalent of 20 mg. relaxin standard. A total dosage of 18 cc. was given over a period of 20 days.

During this time Releasin was the only form of therapy given, except for analgesics, aspirin, and codeine, which were given when necessary for the relief of pain.

Within 48 hours of starting such treatment there was a dramatic reduction in the severity of her pain. After six days of therapy she had her first night of uninterrupted sleep in several months.

This reduction in the severity of pain was maintained throughout the course of treatment. This improvement was paralleled by a reduction in the amount of analgesics necessary.

The following, additional observations were made:

1. There was increased flexibility of the fingers and ability to grasp and lift small objects, whereas previously she could do so only with difficulty.
2. There was an increased sense of general well-being.
3. Reduction in the swelling of the fingers.
4. Formation of a clear line of demarcation on the tip of the index finger, distal to the area of original involvement.
5. Improvement in general strength.

It should be noted that there was some residual pain and swelling, especially of the index finger. After 20 days we felt that we had achieved a maximal response, and since it was not practical to continue this form of therapy on a long-term basis, we discontinued Releasin and started the patient on prednisolone, using an initial dosage of 40 mg. per day. It is of interest that she had a very dramatic response within 48 hours, with complete relief of pain and disappearance of all residual swelling. The fingers healed completely over a period of about two months and it was possible to stop the steroids completely after a period of four months. At this time (January, 1959), she appears to have obtained at least a temporary remission, and there has been no recurrence of the ulcerations.

CASE 2.—A housewife, aged 32 years, was first seen in June, 1955. Her chief complaint at that time was severe pain involving the fingers and hands, precipitated and aggravated by cold. She also gave a history of recurrent ulcerations of the finger tips. The clinical impression at that time was early scleroderma, with Raynaud's phenomenon. A bilateral dorsal sympathectomy was performed with a resulting satisfactory symptomatic improvement.

In the winter of 1958, after brief exposure in subzero weather, she developed ulceration and gangrene of the tip of the right index finger. Her chief complaint was of very severe pain involving the thumb, index, and middle fingers. This pain was so severe as to require meperidine (Demerol), 100 mg. three times per day, for partial relief—before we saw her. This dosage of analgesic was required from Feb. 19, 1958 to April 22, 1958, to keep her minimally comfortable.

On April 22, 1958, she was started on Releasin, 1 cc. intramuscularly, per day. After about three days of Releasin therapy the pain decreased and she no longer required Demerol. Instead, she was maintained reasonably comfortable with the occasional use of acetylsalicylic acid and dextro propoxyphene hydrochloride, Lilly (Darvon).

After two weeks of Releasin therapy, she noted a very definite and dramatic improvement. This was both in the degree of pain and in her sense of general well being.

During the third and fourth weeks of therapy she remained about status quo, however, maintaining her improvement.

On May 29, 1958, Releasin was discontinued. After about three days she had recurrence of severe pain.

Thereafter, she was managed conservatively with analgesics alone. During the next four-month-period a definite line of demarcation appeared and when she was seen on Sept. 28, 1958, the tip of the finger had not completely separated and she was essentially free of pain.

This patient was studied exhaustively from a laboratory standpoint. No significant abnormalities were detected. X-ray study of the gastrointestinal tract was within normal limits.

The final follow-up visit was on Jan. 19, 1959, at which time her finger was healed completely. The minimal sclerodermatous changes in the skin of both hands had not progressed.

Comment

The management of the disabling peripheral vascular complications of scleroderma, Raynaud's disease, etc., poses a tremendous therapeutic challenge. No single form of therapy is uniformly effective. It is interesting to speculate on the cause of the dramatic response to steroids in Case 1. One wonders whether or not there may have been some synergistic effect between the Releasin and the prednisolone.

While relaxin would not be the initial drug of choice, it would appear to be a useful adjunctive measure, and perhaps may offer something to patients who fail to respond to other forms of therapy. Perhaps, also, the combination of Releasin and steroid may offer something to these unfortunate people.

Summary

The use of relaxin in the management of two patients with disabling trophic

ulceration and gangrene, with Raynaud's phenomenon, due in one case to scleroderma-dermatomyositis and in the other to scleroderma, is described. Significant improvement was obtained.

Henry Ford Hospital (Dr. Livingood) (2).

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Cutaneous Meningioma (Psammoma)

Autopsy Findings in a Previously Reported Case

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Cutaneous meningioma is a rare benign tumor first described by Winkler, in 1904.[1] Six additional cases have since been reported.[2-5] Microscopically, cutaneous meningiomas are identical in structure with the common intracranial meningioma or psammoma. The lesion originates in the skin or subcutis, unconnected with intramedullary portions of the nervous system or its membranes. Confirmation of autochthonous origin of the lesion in a given case requires the demonstration that there is no intracranial tumor or any cranial defect with meningeal protrusion to which the origin of the tumor could be ascribed. Intracranial meningiomas eroding the skull and meningiomas located within deeper layers of the scalp unrelated to skin are thus excluded.

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From the Department of Pathology, University of Alberta.

We have previously described a typical case of cutaneous meningioma.[5] The following is a report of the subsequent clinical course and autopsy findings.

Report of Case

Clinical Course.—On Oct. 4, 1955, a cutaneous meningioma (Fig. 1) which had been present for many years was excised from the scalp of a 38-year-old French-Canadian man. It was located 2 in. posterior to the frontal hairline in the midline. Skull roentgenograms and neurological examination by a consultant revealed no evidence of an intracranial tumor.

On Feb. 1, 1958, the patient entered the University of Alberta Hospital with a three- to four-month history of severe throbbing occipital headaches, blurring of vision, insomnia, and episodes of hematuria. There was an antecedent history of benign hypertension of about three years' duration. Findings on physical examination were Grade 4 hypertensive retinopathy with many hemorrhages, exudates, and papilledema; pulse, 88 per minute; blood pressure, 140 mm. diastolic and 220 to 240 mm. systolic. Urinalysis: acid reaction, specific gravity

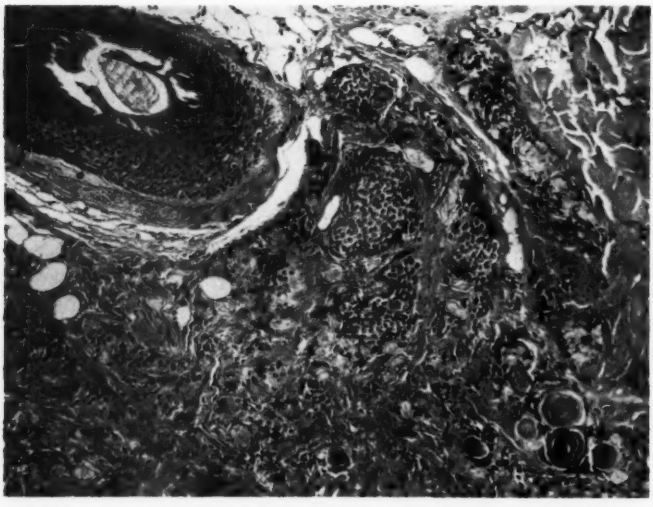

Fig. 1.—Cutaneous meningioma showing nests of meningothelial cells and psammoma bodies in relation to a hair follicle.

1.020, protein 3+, glucose negative. Urinary sediment contained 1 or 2 pus cells and many red cells per high-power field. Hemoglobin 13.5 gm. %. Hematocrit 42%. White cell count 8,400 per cubic millimeter. Serum electrolytes were normal. Blood urea nitrogen 17 mg. %. Kahn test negative. The two-hour phenolsulfonphthalein excretion was 35%, but the intravenous pyelogram was normal. A phentolamine (Regitine) test was negative.

Therapy included a salt-free diet, phenobarbital (Luminal), ½ grain (32.5 mg.) t. i. d., and reserpine (Serpasil), 0.5 mg. q. d. The blood pressure fell to 140 to 155 mm. systolic and 90 to 100 mm. diastolic, and erythrocytes disappeared from the urine. The funduscopic picture did not change. He was discharged from the hospital on Feb. 4, 1958.

Notwithstanding continued administration af antihypertensive drugs, headache and marked hypertension recurred. The patient was readmitted to the University of Alberta Hospital Dec. 3, 1958, with oliguria and convulsions. Physical examination showed facial and periorbital edema, Grade 4 papilledema, dry tongue, blood pressure 270/120, pulse 120 per minute, muscular twitching, and hyperreflexia. Chest roentgenograms showed marked cardiac enlargement. Urine volume ranged from 125 to 350 cc/24 hours. Urinalysis: acid reaction, specific gravity 1.014, protein 2+, glucose negative. Urinary sediment contained 30-40 pus cells and 8-15 red cells per high-power field. Hemoglobin, 8.0 gm. %. Hematocrit 24%. Erythrocyte sedimentation rate 50 mm. per hour (Wintrobe). White cell count 10,800, with 93% polymorphonuclear neutrophils. Blood urea nitrogen 147 mg. %. Serum calcium 9.0 mg. %; phosphorus 9.2 mg. %; creatinine 19.6 mg. %.

On Dec. 4, the patient developed incipient left ventricular failure. The blood urea nitrogen reached 238 mg. %, and on Dec. 7 uremic coma supervened accompanied by uremic frost and a pericardial friction rub. Death occurred the following day.

Autopsy Findings.—The body was that of a muscular, 6 ft., 230 lb., white man. The pleural cavities contained a combined volume of 300 cc. and the pericardium 40 cc. of watery fluid. The heart (720 gm.) showed left ventricular hypertrophy. There were no valvular deformities. The left and right lungs (710 and 1,040 gm., respectively) were congested and edematous. The kidneys (each 160 gm.) had granular surfaces from which the renal capsules stripped readily. Microscopically, there was marked hyaline arteriosclerosis of renal afferent arterioles; interlobular branches showed advanced concentric fibrocellular intimal hyperplasia. Scattered glomeruli showed periglomerular fibrosis and occasional glomeruli were hyalinized. The right adrenal gland (15 gm.) contained a 1 cm. gray-brown nodule (Fig. 2*A*) with the microscopic structure of a pheochromocytoma (Fig. 2*B*). Reflection of the scalp revealed no residual tumor at the site of previous excision of the cutaneous meningioma[6] and no defect in the underlying cranial vault. The brain (1,550 gm.) showed no abnormality other than slight flattening of cerebral gyri. There was no intracranial tumor and dura and meninges were normal. The autopsy revealed no findings suggestive of multiple neurofibromatosis.

Comment

The case presented represents the only instance in which a cutaneous meningioma

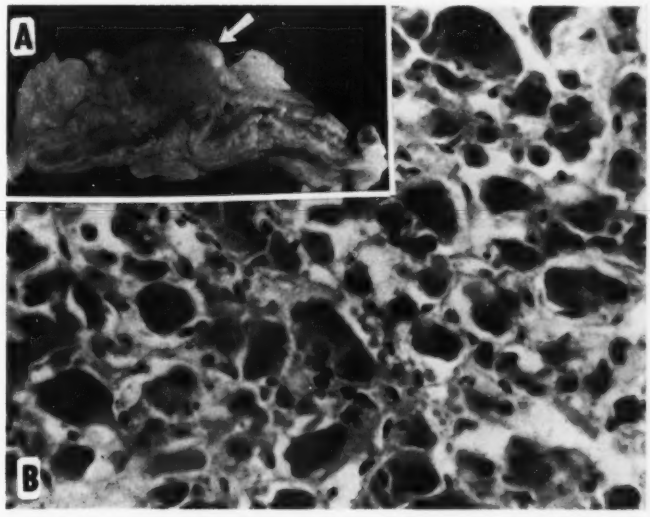

Fig. 2.—*A*, pheochromocytoma of right adrenal gland (arrow). *B*, pheochromocytoma containing pleomorphic tumor giant cells.

has been authenticated by autopsy study, with fulfillment of diagnostic criteria previously proposed.[5]

Harvey and associates [6,7] have presented experimental evidence to suggest that the pia-arachnoid membrane is of neural crest origin, and that arachnoid cells and Schwann cells are closely related histogenetically. Cutaneous meningiomas have been thought to arise either from heterotopic arachnoidal elements sequestrated along lines of closure of the fetal skull and spine or from neuroectodermal sheath cells of cutaneous nerves.[6]

The presence of a pheochromocytoma of the adrenal gland in a patient with a cutaneous meningioma raises the problem of whether the concurrence of two tumors of neurocctodermal origin may be other than fortuitous.[8] The occurrence of both meningioma and pheochromocytoma, as well as other neuroectodermal tumors, is recognized in neurofibromatosis.[9] The possibility arises that the cutaneous meningioma in the present case may have been part of a neuroectodermal tumor complex of which another manifestation was a pheochromocytoma. Such a combination might represent a forme fruste of some hamartial complex analogous to neurofibromatosis. Interesting in this connection is the fact that Winkler's case had multiple cutaneous meningiomas and scoliosis.[1] However, the characteristic stigmata of von Recklinghausen's disease have never been described in association with cutaneous psammoma, nor was there any evidence of neurofibromatosis clinically or at autopsy in the case herein described.

Summary

The cutaneous meningioma is a specific tumor which requires differentiation from tumors of identical microscopic structure having connection with the meninges or their extensions. The present report concerns the terminal clinical course and autopsy findings in a previously reported case. The finding of both a pheochromocytoma of the adrenal gland and a cutaneous meningioma introduces the possibility that these are manifestations of a neurocutaneous syndrome.

Dr. A. M. Edwards provided clinical data pertaining to this case. Mr. Eric Beamont prepared the photomicrographs.

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Ichthyosis Follicularis

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Ichthyosis follicularis occupies a sentence to a few paragraphs in most representative textbooks of dermatology. Our interest in this entity was recently stimulated when we had the opportunity to study two patients who presented cutaneous abnormalities characteristic of ichthyosis follicularis. A study of our cases and of the very few reports in the literature inspired a critical analysis of this disease.

Report of Cases

CASE 1.—An 8-year-old, mentally retarded, Negro boy was seen in dermatologic consultation on April 19, 1958, at the Rosewood State Training School because of extensive alopecia.

The family history revealed no maternal abnormalities. Two paternal cousins suffered from mental illness of an unknown nature, and one paternal cousin was epileptic. The patient's two siblings were without mental retardation or cutaneous abnormalities.

The pregnancy was free of complications, and the delivery was noninstrumental. Scalp hair was absent at birth. The child's development was retarded; he could not sit alone until the age of 1 year and was unable to walk until the age of 4 years.

Physical examination upon admission to the Rosewood State Training School on April 2, 1958, showed the following pertinent findings. His height was 36½ in. (normal minimum for patient's age is 45 in.). There were photophobia, conjunctivitis, esophoria, and horizontal nystagmus. The teeth were well developed, though numerous caries were present. An umbilical hernia was present.

The outstanding cutaneous manifestation was the complete absence of hair; there was none on the scalp, eyebrows, eyelashes, face, torso, or extremities. There was also typical large quadrilateral ichthyotic scaling over much of the body, particularly marked on the extensor aspects of the upper and lower extremities and on the abdomen. In addition, there were many discrete normal-colored keratotic follicular papules over the scalp, nose, cheeks, neck, shoulders, and back. These scattered lesions were rather symmetrically distributed and gave a feeling of roughness (nutmeg-grater-like) to palpation. The palms and soles were normal. All fingernails were present but were distorted and deformed. Upon emotional stimulation, there was considerable evidence of perspiration (Figs. 1, 2, 3).

The urinalysis was negative. Hemoglobin was 10.5 gm. %. The white blood cell count was 10,350 per cubic millimeter and the red blood cell count was 3,480,000 per cubic millimeter, with evident anisocytosis. Blood serologic tests for syphilis were negative. The stool was negative for ova and parasites. Roentgenologic study of the skull was normal without evidence of intracranial calcification. X-ray examinations of the chest and of the lumbar spine and an intravenous pyelogram were normal. X-ray examination of the long bones showed epiphyseal age in the 5- to 7-year range.

Fig. 1.—Generalized alopecia and ichthyosis vulgaris of Case 1.

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From the Subdepartment of Dermatology, Department of Medicine, The Johns Hopkins Hospital and School of Medicine, Baltimore, and from the Rosewood State Training School, Owings Mills, Md.

Fig. 2.—Ichthyosis of thighs and legs of Case 1.

The intelligence quotient, according to the Binet test, was 31, or in the imbecile class. His reactions, however, led the evaluating psychologist and other observers to believe that his potential was higher.

Four biopsy specimens were obtained, were studied serially, and showed essentially the same microscopic findings. They were taken from a typical area of ichthyosis on the left thigh and from the scalp, the right shoulder area, and the center of the forehead. The stratum corneum was thickened and loose throughout with an increase of the hyperkeratosis about the orifices of the follicles. The granular layer was normal. The rete was thin, and some cells of this layer showed considerable perinuclear edema, such as is not infrequently seen in epidermal nevi. Some inactive abortive hair follicles were present; they possessed no bulbs, and their bases were in the dermis rather than in the subcutis. A few abortive hairs were present. One of the most remarkable findings was the complete absence of sebaceous glands or cells in all serial sections. Many normal eccrine sweat glands were seen. In the upper third of the dermis there was a mild infiltrate of small mononuclear cells, predominantly perivascular and associated with dilated capillaries (Figs. 4, 5, and 6).

This patient died Oct. 7, 1958, of an amebic hepatic abscess. Postmortem microscopic examination of the axillary skin showed essentially the same findings as the biopsy specimens. In addition, many normal apocrine sweat glands were present.

Case 2.—A 3½-year-old white boy was referred to the Dermatology Clinic of The Johns Hopkins Hospital Aug. 31, 1958, because of alopecia.

The family history was noncontributory. He had no siblings. His delivery was without complications after an uneventful pregnancy. At birth, no hair was noted on any part of his body. His growth and development were normal except for the absence of hair until 2½ years of age, when fine blonde hair first appeared on the parietal areas.

Physical examination was essentially normal except for the skin. He had universal alopecia except for sparse hair over the scalp and fine blonde hair on the parietal areas of the scalp. There was no hair elsewhere on the body and there was complete absence of eyebrows and eyelashes. On the scalp, neck, face, and on the extensor aspects of the upper and lower extremities there were many scattered discrete normal-colored keratotic follicular papules distributed rather symmetrically. Palpation gave a nutmeg-grater-like feel. The palms and soles, as well as all nails, were normal. There was no evidence of ichthyotic scaling. Sweating was easily elicited. Photophobia was marked (Fig. 7).

A biopsy specimen was obtained from the scalp and sectioned serially. The stratum corneum was thickened throughout and was loose with an increase of the hyperkeratosis about the follicular orifices. The granular layer was normal, and the rete was thin. The few hair follicles present had no bulbs and only a few abortive hairs. In only one section were a few sebaceous cells seen. Many normal eccrine sweat glands were present. In the upper third of the cutis there was some vascular dilatation with a mild infiltrate of small mononuclear cells, predominantly perivascular (Figs. 8 and 9).

Comment

Though there are somewhat similar descriptions in the literature prior to that of Lesser's,[1] in 1885, he appears to have been

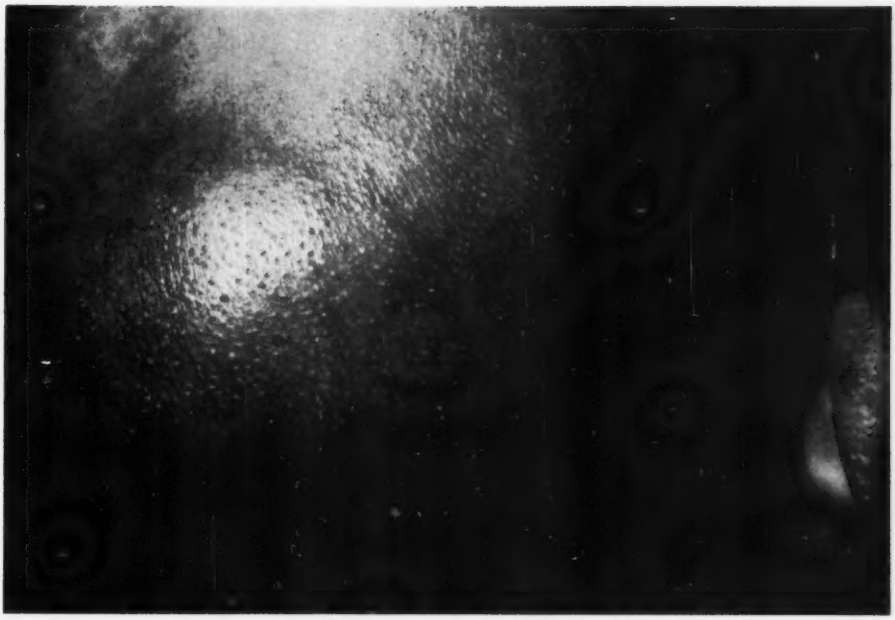

Fig. 3.—Alopecia and keratosis pilaris of scalp of Case 1.

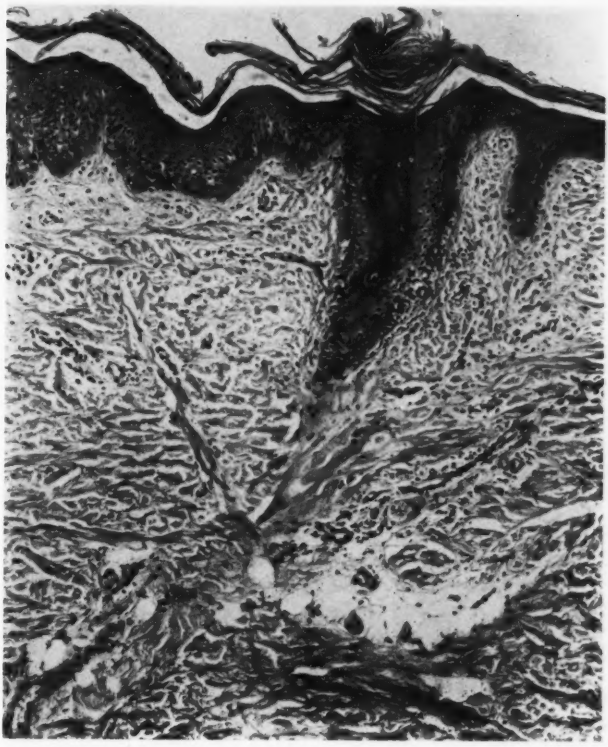

Fig. 4.—From thigh of Case 1. Hyperkeratosis of follicular orifice and intervening skin. Normal granular layer. Abortive hair follicle. Perivascular small monocytic infiltrate; × 100.

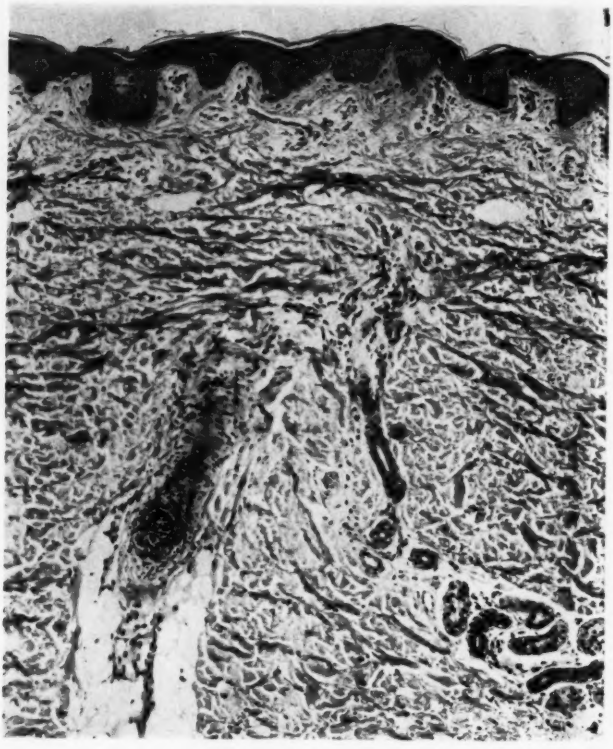

Fig. 5.—From scalp of Case 1. Abortive hair follicle. Normal eccrine sweat glands. Absence of sebaceous glands; × 100.

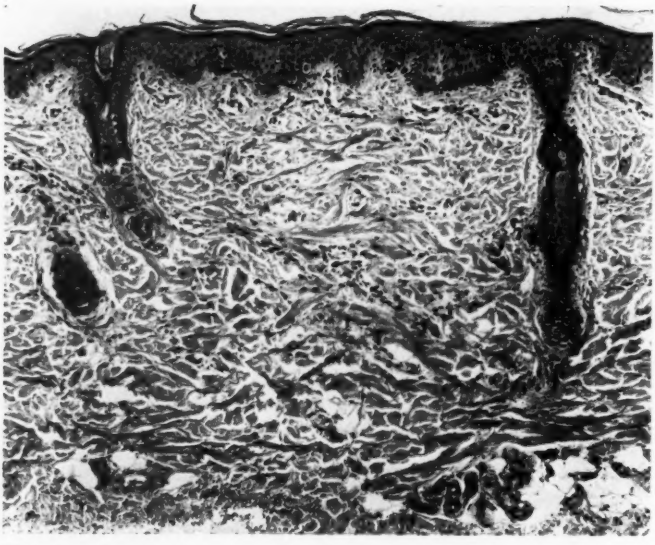

Fig. 6.—From forehead of Case 1. Hyperkeratosis of follicular orifice and intervening skin. Abortive hair follicles and hair. Normal eccrine sweat glands. Perivascular small monocytic infiltrate. Absence of sebaceous glands. Reduced 15% from mag. × 100.

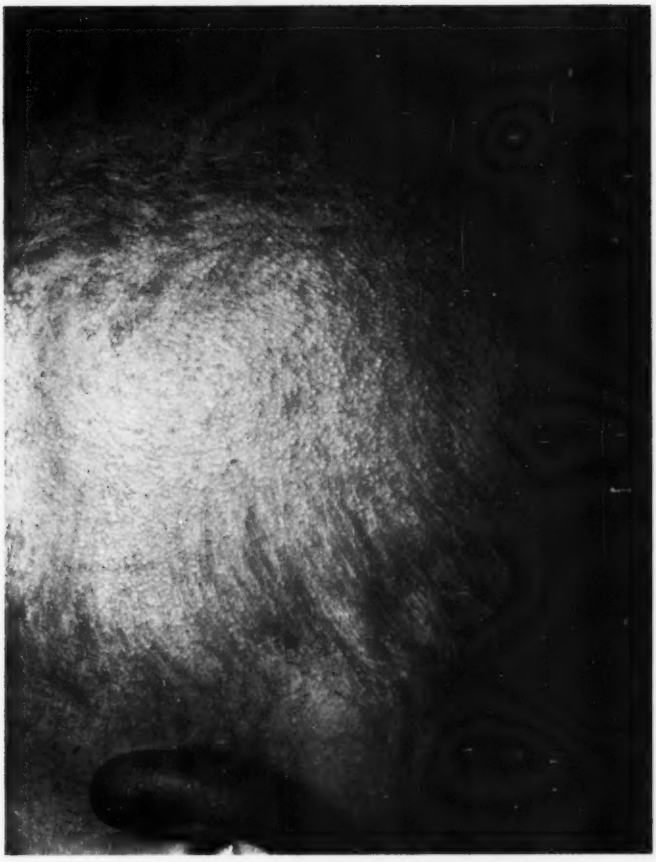

Fig. 7.—Incomplete alopecia and keratosis pilaris of scalp of Case 2.

the first to use the term ichthyosis follicularis for this dermatosis. He described a 6-year-old boy who had no scalp hair at birth and in whom a scanty growth appeared during his third year. He had keratotic follicular papules over the extensor aspects of the extremities and on the face over the brows and nose. The flexor surfaces and the trunk were much less affected, and the palms and soles were entirely free. On the scalp, where there was scanty hair growth, follicular papules were present. The eyebrows were entirely absent and the affection was very marked here. Palpation produced a sensation like that caused by the "prickly" surface of a rose-leaf." There was no mention made of ichthyosis vulgaris anywhere. It was Lesser's belief that the keratotic follicular papules represented a form of ichthyosis which was limited strictly to the follicles.

MacLeod,[2] in 1909, published a detailed study of ichthyosis follicularis in which he reviewed the literature of similar dermatoses and reported three cases. Three brothers, aged 19, 13, and 10 years, respectively, presented a strikingly similar appearance owing to the absence of eyebrows and eyelashes, the more or less complete baldness of the scalp, and the presence of trachoma and conjunctivitis. The hairy system was the part chiefly affected with the hairs replaced by pinhead-sized normal-colored papules surmounted by horny spines. These were most marked on the extensor surfaces of the upper arms, back and sides of neck,

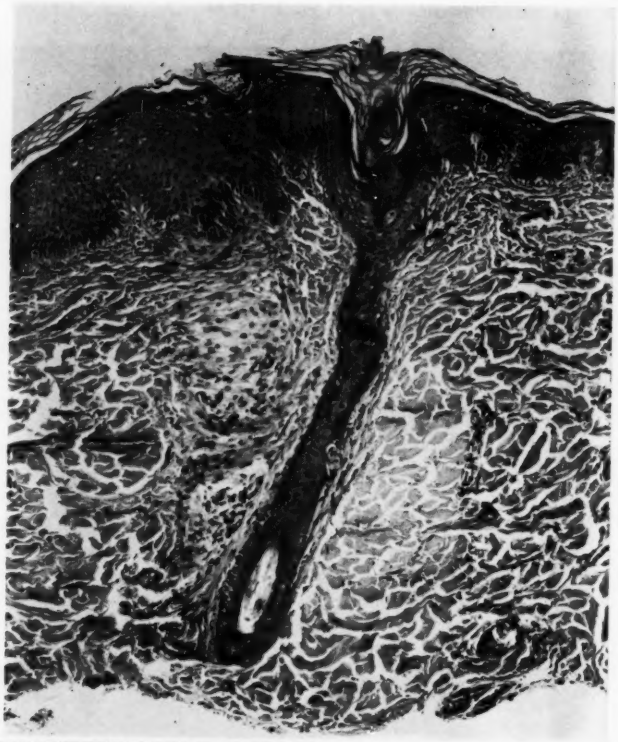

Fig. 8.—From scalp of Case 2. Hyperkeratosis especially marked at follicular orifice. Abortive hair follicle and hair. Few sebaceous cells; × 100.

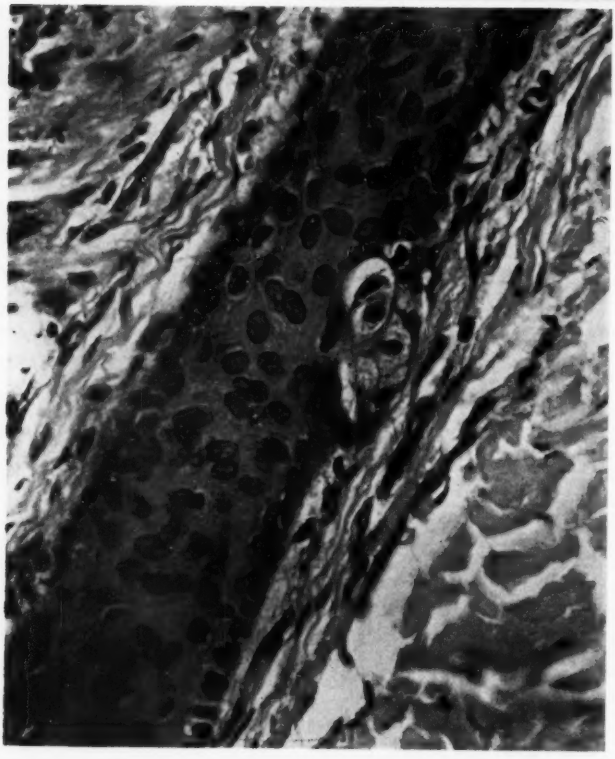

Fig. 9.—Enlargement of area of Figure 4, demonstrating the few subaceous cells present; × 500.

and the back. They were irregularly distributed and tended to be roughly symmetrical. In addition to the follicular lesions, the skin was dry and harsh, typical of ichthyosis vulgaris, especially on the buttocks, thighs, and knees. The sweat glands were not affected, since the patients perspired freely on exertion.

MacLeod studied the histological picture of a biopsy specimen removed from the neck of one of his patients. There was hyperkeratosis with accentuation of this phenomenon affecting the funnels of the follicles. The granular cell layer was intact. There was some thinning of the rete. The lower two-thirds of the hair follicles was atrophied and in some of them pieces of atrophied hairs were noted. The sebaceous glands were absent. The coil glands were present. The underlying corium presented a flattening of the papillary layer, a slight dilatation of the blood vessels in the neighborhood of the follicles, and an infiltration of small cells about the capillaries and the follicles. These microscopic findings were virtually identical to those seen in our cases.

Manson[3] described under the caption, ichthyosis follicularis, two brothers and one sister with incomplete congenital alopecia of the scalp and with keratosis pilaris-like lesions. Marzollo[4] reported a patient who had ichthyosis vulgaris and alopecia. There was partial alopecia of the scalp with keratotic, follicular, comedo-like papules on the alopecic areas. Similar papular lesions were present on the chest. Considerable ichthyosis vulgaris was noted especially on the extremities. Though the eyebrows were thick, there was little hair on the bearded areas, the axillae, and genital regions, and none on the torso.

Lesser,[1] MacLeod,[2] and Manson[3] reported their cases under the caption "ichthyosis follicularis," while Marzollo[4] titled his case report "Ichthyosis Vulgaris and Alopecia." Our cases are identical, and in addition there are others that have been reported simply as cases of "congenital alopecia." Some, but not all, patients with congenital alopecia have an associated keratosis pilaris. Such cases have been reported as "congenital alopecia" by Ziegler,[5] Watson,[6] Oliver and Gilbert,[7] Chiaramonte,[8] and Birke,[9] for example, with a syndrome identical with those reported as "ichthyosis follicularis"; their patients had keratosis pilaris lesions as well as congenital alopecia.

This disease is a heritable disorder which occurs at birth and at times appears in siblings. Clinically, it is characterized by more or less alopecia of the scalp and any or all other hairy areas, and by the presence of keratosis pilaris-like lesions in some regions where there is absence of hair. Microscopically, the usual findings are those noted by MacLeod[2] and Marzollo[4] and confirmed by us in serial sections. There is hyperkeratosis affecting the mouths of the follicles and also the intervening skin. The granular layer is intact. The rete is thin and the interpapillary processes flattened. The hair follicles are atrophic with abortive hairs sometimes seen. Sebaceous glands are absent or virtually so. None was seen in serial sections of four biopsy specimens and one autopsy specimen of our first patient and only a few sebaceous cells in our second. The eccrine and apocrine sweat glands are normal. There is some dilatation of blood vessels in the upper third of the cutis, as well as perivascular infiltration consisting mainly of small mononuclear cells.

Ichthyosis follicularis is a misnomer. This is not an ichthyotic condition limited to the follicles since the hyperkeratosis affects the intervening skin as well as the follicular orifices. It is difficult to conceive of a situation in which there is retardation of desquamation at the follicular orifices but not in the intervening skin. The essential feature is the congenital absence or marked decrease of the pilosebaceous system.

It is a congenital ectodermal defect of the pilosebaceous system. The poorly developed follicles, the relative absence of hairs, and the virtual complete absence of sebaceous glands comprise the essential pathology. The hyperkeratosis and the mild superficial in-

flammation of the cutis are probably secondary to the absence of sebum which is so necessary in maintaining adequate hydration of keratin.[9] It is recognized that the lack of sufficient sebaceous excretion may lead to fissuring, infection, pruritus, decreased resistance to friction and pressure, and greater intolerance for fat-solvent chemicals.[10] Clinically, this disease is manifested from birth by alopecia and the presence of keratosis pilaris-like lesions. It must be noted, however, that not all patients with congenital alopecia with or without keratosis pilaris fit into this category; it comprises only those that demonstrate a congenital pilosebaceous defect microscopically.

The association at times with ichthyosis vulgaris as in MacLeod's,[2] Marzollo's [4] and our first case is probably based on a common genetic cause. The heritable nature of ichthyosis is undoubted [11,12] and its occasional association with idiocy, epilepsy, infantilism, etc. is well recognized.[13] This disorder, however, occurs usually without associated ichthyosis vulgaris. In fact, Lesser's [1] original description mentioned no such association and, as already stated, his original idea was to hypothesize that the disease was one in which there occurred ichthyosis of follicles only.

Summary

The literature concerning ichthyosis follicularis is reviewed critically. Two cases which correspond to this dermatosis are reported. There are other reports of similar cases under the caption of congenital alopecia. The term ichthyosis follicularis is a misnomer and should be eliminated. This disease is a congenital ectodermal defect of the pilosebaceous system.

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Growth and Development

VI. Changes in Skin Color of Fifty-One Negro Infants from Birth Through Three Years of Age, as Related to Skin Color of Parents, Socioeconomic Status, and Developmental Quotient

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The measurement of skin color has provoked considerable interest and research in recent years. In general, attention has been concentrated upon the most efficient manner of measuring the degree of pigmentation as a means of assessing actual color content. Medically, the problem has been one of ascertaining how and to what degree pigmentation affects either the recognition or the course of various diseases, as well as how specific treatments such as infrared and roentgenotherapy are influenced by skin color. A recent paper in this series [1] discussed a phase of the question of skin color upon which less emphasis has been placed: the relation of skin color in newborn Negro infants and their parents to certain physical, psychological, and social factors. It was pointed out at that time that the question is complicated by the fact that Negroes tend to grow darker with age. Niedelman [2] states, "Negro infants are not so dark at birth as they become later . . . the rate of darkening in newborn Negro infants varies individually. The pigmentation of the skin in a Negro does not reach its maximum until puberty, after which it decreases in intensity." Herskovits [3] states, ". . . all indications go to show that the pigmentation of the Negro becomes steadily darker with age."

Lasker [4] has investigated the seasonal changes in skin color among a group of young American white adults and found, "Seasonal differences caused by exposure to the sun are an appreciable factor." He expresses the opinion that this factor must be taken into account in studies of racial differences. However, while seasonal variations are undoubtedly an important consideration, it would seem pertinent to document any changes in skin color which appear on a longitudinal basis, especially in a group such as the Negro where there is a wide range of variation in degree of pigmentation. No such study could be found in the literature. The present report, therefore, was undertaken to provide some preliminary information in this area.

It is the purpose of this paper to report on skin color changes in Negro infants from birth through three years of age, and to compare skin color at birth and skin color at 2½-3 years of age with skin color of parents, socioeconomic status, and with a developmental evaluation of the child at the two extreme age periods (birth and 2½-3 years).

Methods and Materials

Data for this study are taken from a five-year longitudinal study of the anatomical, physiological, and psychological factors affecting the growth and development of Negro infants and children, detailed reference to which has already appeared in print.[1,5-7] The 51 children upon whom this report is based represent an exclusive group of loyal participants who had been seen in the research clinic at all scheduled intervals from birth through 3 years of age. They were seen at three-month intervals up to 2 years of age, and at six-month intervals thereafter. Thus, there are available on each infant eleven consecutive skin-color determinations for analysis.

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Measurement of Skin Color.—Skin color determinations were made through the use of a color chart with nine positions, ranging from (1) very light to (9) very dark. The description of the chart and its use can be found detailed in a previous paper by Horton and Crump.[1] All determinations of infants' skin color were made by the psychologist in the research clinic, while determinations of parents' skin color were made by the medical social worker. The method of measurement was tested for both validity and reliability and found to be acceptable for use.

Lasker[6] states, "In selecting sites of skin for study three considerations present themselves: the areas should be free of pigmented hairs, they should be clean, and they should be accessible and present a flat surface to the search unit." In this study, skin color of the mother was obtained by using the inner aspect of the arm just above the elbow. The father's skin color was obtained in most instances by having the mother select his color from the color chart, owing to the general inaccessibility of fathers to members of the research staff. Infants' skin color is measured in three zones, only one of which will be considered here. Determinations are made from the ear lobe, the base of the fingernail, and the cheek. It is well known that pigmentation is rarely uniform on all body surfaces; thus, three different determinations are taken on children in order to measure any differences which may exist. This paper, however, will use only the determination made from the ear lobe. This is the area which is generally presumed to be the closest indication of what the final color will be.

Socioeconomic Status.—The socioeconomic rating used here divides the study population into four groups from I (low) to IV (high). The evaluation is derived from interviews and observations in the home. The method of attainment and factors included are fully described by Crump and his associates.[6]

Developmental Evaluation of the Child.—Although some developmental evaluation of the child is made at each follow-up appointment, this paper is concerned only with the evaluations made at birth and at 30 months. At birth, a battery of reflex tests is given to the infant, including nine reflexes, each of which is scored on a five-point scale ranging from 0 for "absent" to 4 for "very marked."* At 30 months, the Gesell Developmental Schedules[9] are used. These schedules measure infant and child development in four areas: motor, adaptive, language, and personal-social. The end result is a general maturity index which, with use of the Gesell method, must frequently be expressed as a range (e. g., 24-30 months). Because it was felt that a specific figure, roughly comparable to an intelligence quotient in its implications for development, would more adequately fulfill the requirements of this study, a scale was devised which gives a precise figure representing the level of development; these four figures are summed and the sum divided by four to arrive at the general maturity level. Finally, the figure representing the general maturity level is divided by the child's chronological age and the quotient multiplied by 100, yielding the "developmental quotient" referred to hereafter. The Gesell general maturity index correlates highly with the general maturity level as developed here (r=0.94 at 30 months), which in our opinion justifies the use of the original scale.

* See Horton and Crump[1] for a list of the reflexes included.

Results

Skin Color Changes from Birth Through 36 Months.—Table 1 presents the changes in skin color *group* (light, medium, dark), which occurred between birth and 30 months for 23 children (no 36-months' color determination available), and between birth and 36 months for 25 children.† For the total of 48 children, 75% remained in the same color group between birth and 2½-3 years of age. Only 2 of the 48 children became lighter during this three-year period. Both these infants shifted from "dark" to "medium."

Much more shifting is observed when both inter- and intragroup changes are noted. As indicated in Table 2, only 27.1% of the children were the same *shade* at 30 or 36 months that they were at birth. Over half of them became one or more shades darker. Actually, if each of the nine positions on the color chart is considered a

† For two infants, no skin color determination was made at birth, and for the third, no determination was made at 30 or 36 months.

TABLE 1.—*Changes in Skin Color Group Between Birth and Thirty-Six Months* *

Changes in Skin Color Group	Age of Child: 30 Mo., N=23	36 Mo., N=25	Total, N=48
No change	87.0	64.0	75.0
Lighter	--	8.0	4.2
Darker	13.0	28.0	20.8
Total	100.0	100.0	100.0

* In percentages.

TABLE 2.—*Changes in Specific Skin Color Between Birth and Thirty-Six Months* *

Change in Specific Skin Color	Age of Child: 30 Mo., N=23	36 Mo., N=25	Total, N=48
No change	34.8	20.0	27.1
Lighter	13.0	28.0	20.8
Darker	52.2	52.0	52.1
Total	100.0	100.0	100.0

* In percentages.

TABLE 3.—*Individual Changes in Color, by Color at Birth*

Color Change by 2½-3 Yr.	Color at Birth: 3	4	5	6	7	8	Total
No change	—	5	3	4	1	—	13
1 shade lighter	2	—	1	4	1	1	9
2 shades lighter	—	—	—	—	1	—	1
1 shade darker	—	5	8	3	—	—	16
2 shades darker	—	2	4	2	—	—	8
3 shades darker	—	—	1	—	—	—	1
Total	2	12	17	13	3	1	48

step, only nine children moved more than one step during the 2½- to 3-year period. Eight of these became two shades darker, while one became two shades lighter. The greatest shift in color occurred for a child who moved from shade 5 at birth to shade 8 at 36 months.

It might be hypothesized that variation in color is affected by original color, i. e., whether a child grows lighter or darker is in part a function of the original degree of pigmentation. When changes in shade are analyzed in terms of the specific shade at birth, it is interesting to note that of the

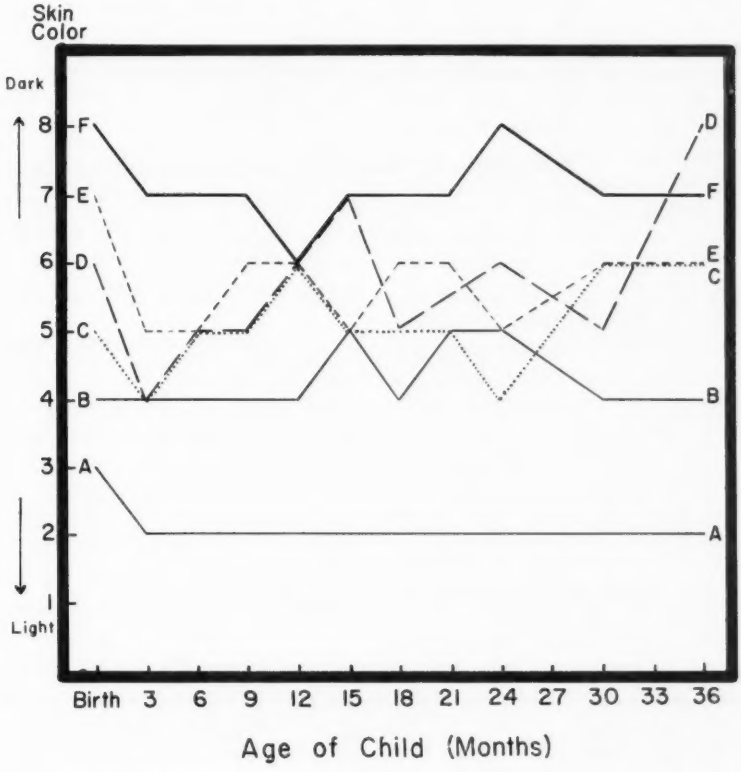

Fig. 1.—Skin color of six Negro children from birth through 36 months.

six infants considered either "light" or "dark" at birth, five of them were recorded as lighter by 3 years of age, while one remained the same shade. In contrast, only 4 of the 42 children whose color determinations were 4, 5, or 6 ("medium") at birth, were lighter by 3 years of age. Approximately one-fourth (26.2%) of these children remained the same shade. Specific changes in color are presented in Table 3.

This is not the complete picture, since the color ratings fluctuate at points between birth and 30 or 36 months, but the terminal rating is what is being considered here. The correlation between skin color at birth and skin color at 30 months is 0.6297 for 44 children. Figure 1 presents changes in skin color from birth through 36 months for one child chosen at random at each color position noted at birth. The fluctuation and overlapping from interval to interval is apparent.

Comparison of Children with Parents.—The earlier study of skin color in this series,[1] which was based on a much larger group of subjects, resulted in the conclusion, "The vast majority of Negro infants [being considered] are neither significantly lighter nor darker than their parents." Correlation coefficients for skin color of mother and infant and for skin color of father and infant were 0.3001 and 0.305, respectively. Table 4 presents the correlation coefficients for the relationship between parents' skin color and infants' skin color at birth and at 30 months, based on the smaller group being studied here.

Both at birth and at 30 months, the color of the child shows higher correlation with that of the father than with that of the mother, although statistically there is no significant difference between the correlation coefficients for the two parents at either age level. The correlations are higher at 30 months than at birth for both parents.

Socioeconomic Status and Skin Color.—Some association was found earlier between skin color of parents and socioeconomic status.[1] Since the child's socioeconomic rating is necessarily the same as his parents', and since children tend to be smiliar to their parents in color, it would follow that there would be some degree of association between socioeconomic status and color of the child. The correlation coefficient $= -0.3098$, indicating that the nature of the existing relationship is such that high socioeconomic status is associated with lighter color. The association is not, however, statistically significant.

Developmental Evaluation and Skin Color.

Mean developmental quotients at 30 months are shown in Figure 2 by skin color group.

No relationship is apparent. The correlation coefficient between these attributes is -0.183, which is not statistically significant. Neither was there apparent a significant relationship between reflex maturity at birth and skin color.[1] In view of these findings, it appears in this study that through the age of 30 months development of the child is independent of skin color.

Summary and Conclusions

It would be necessary to observe a much larger group of children before any final conclusions concerning changes in skin color with age can be stated. There are, however, trends and relationships which emerge from data presented in this study that can be summarized and filed to await confirmation

TABLE 4.—*Correlations of Parents' and Children's Skin Color*

	Mother			Father		
Age Level of Child	*r*	*N*	Level of Stat. Sig.	*r*	*N*	Level of Stat. Sig.
Birth	0.1909	48	None	0.3481	40	0.025
30 mo.	0.4045	49	0.005	0.6646	41	0.005

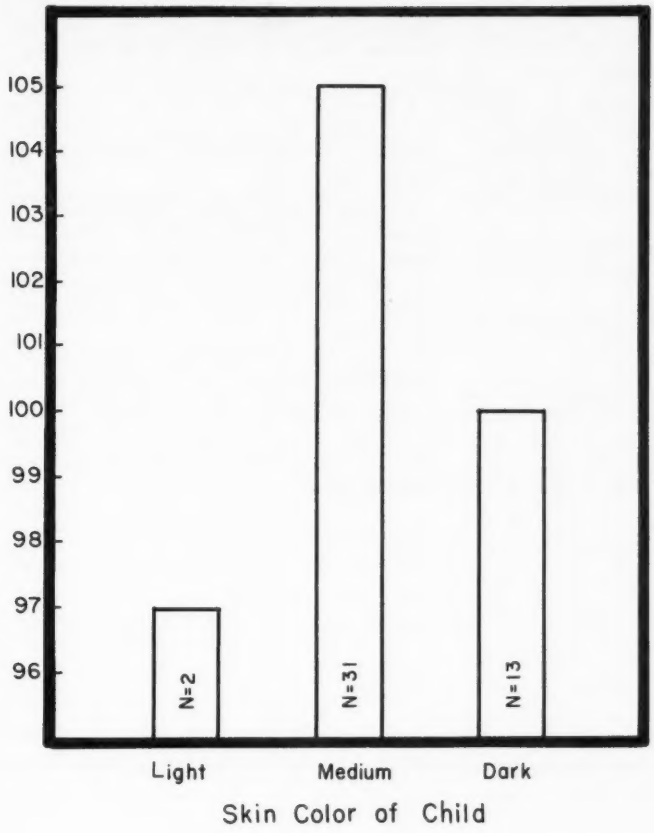

Fig. 2.—Mean developmental quotient at 30 months, by skin color group.

or refutation based on more extensive observation.

1. By the time a child is 3 years old, it is likely that his *specific* color will have changed from what it was at birth. However, about three-fourths of the children in this study remained in the same color *group*.

2. Generally, more fluctuation is observed among children who are in the "medium" color group. This may be due to the fact that it is more difficult to make consistently precise color determinations in the middle range than at either extreme.

3. The correlation of children's color with that of their parents is higher at 30 months than at birth, and higher between children and their fathers than between children and their mothers.

4. Some indication is found that children of parents of higher socioeconomic status tend to be lighter in color, but the relationship is not statistically significant.

5. No association is apparent between psychological development of the child and skin color.

It is extremely doubtful that such changes in skin color as were observed in this study would be visible or discernible to the untrained eye. Although considerable fluctuation and variation was observed from one period to another, in the final analysis, major changes were few. It may be that the color of the ear lobe at birth is very close to the color it will have later, or it may be that color changes are greater in magnitude after the age of 3 years.

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Ionizing Radiations in Industry

Their Uses and Potential Dangers

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Few of us realize the great extent to which ionizing radiations are being used in industry in this country today. For example, an x-ray beam assures you of getting a full can of beer. If your cigarette is "easy on the draw," it is because its density is radioactively determined and controlled. Radioisotopes alone are saving U. S. industry millions of dollars annually through improving processes. Also, three atomic reactor plants in different parts of the United States are already furnishing heat and electricity for homes and industry. More than 300 industrial reactor plants are planned for the immediate future.

We are in the midst of a new industrial revolution, an atomic revolution. Even though the first sustained nuclear reaction was achieved barely 16 years ago, atomic industry is sweeping the country. The great increase in its use and the increasing number of persons exposed to ionizing radiations may result in an increased incidence of radiodermatitis, either acute or chronic, and other radiation injuries.

As dermatologists, we must know the uses and potential dangers of ionizing radiations in industry so that we will be alert to the possibility of radiation injury in patients we see in daily practice. We should also be well informed on the subject of radiation protection, so that we can assist local, state, and federal authorities in solving the public health problems which will arise from increasing use of atomic energy in industry, agriculture, and medicine.

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Uses

For many years, x-rays and the γ-rays of radium have been used in a few industries. Reactor-produced radioisotopes are a great boon to industry. They are much more economical and infinitely more versatile than x-rays and radium for industrial purposes. Fisher, in his recent report, "You and the Obedient Atom," [1] provides some interesting statistics. At present, over 900 radioisotopes are available for commercial use, which will give ionizing radiations especially suitable for particular jobs or processes in industry. Oak Ridge Laboratory made over 14,000 shipments in 1957. Nearly 1,700 industrial firms are licensed by the Atomic Energy Commission to use radioisotopes. Among medical institutions and physicians there are approximately 2,000 licensees. More than a million patients are being treated each year. And yet, the biggest use of radioisotopes is in scientific research, where they are inaugurating a new era.

The applications of radioisotopes are many, and new uses are being discovered every day. Co^{60}, Cs^{137}, and other γ-emitters have largely replaced x-rays and radium in testing metal objects for structural defects.[2] Radiographic testing has no doubt been used to check all of the welds on the airplane you ride in and to locate cracks in the cement walls of your large office building.

A radioactive thickness gauge rolled the sheets of your morning newspaper to a uniform thickness. The radioactive material is placed below the sheet coming off the

rollers, and above it is a Geiger counter whose signal automatically adjusts the roller settings to maintain an even thickness without touching, stopping, or cutting the rolling sheet. Plastics, rubber, aluminum foil, and steel are all rolled in this way.[2]

Radioactive liquid level gauges have many uses. One of them is to signal the safe level of molten metal in a sealed cupola. Co^{60} is placed on one side of the cupola and a Geiger counter on the other. There is a sharp decrease in the intensity of the beam when the molten metal reaches this level and comes between the cobalt source and the detector.[2]

Recently, γ-emitting isotopes have been used to determine the denseness and, therefore, the firmness of sites for aircraft runways, road beds, and dams.

Oil companies use radioisotopes to mark an interface between two different grades of oil or gasoline transported hundreds of miles through the same pipe line. At the terminal, the radioactive interface is quickly detected without sampling, and the oil behind it is diverted to the proper channel.

A plumber may put I^{131} into your water line and find the leak with his Geiger counter without tearing up the whole cement floor.

By far the most important application of radioisotopes is their use as tracers. Since radioactive atoms behave chemically exactly like their stable counterparts, and since they emit identifying radiations, they can be used to trace the fate of stable elements through complex processes.

Tracer analysis is useful in determining the distribution of a particular element in a variety of end-products. For example, steel manufacturers found that they could use cheap pyrite coal (containing sulfur, which is an impurity in steel) by using S^{35} to trace the fate of sulfur in the coal-coke process.[2] In this way, they found that the sulfur was not transferred to the steel.

Isotope dilution analysis is used to determine the amount of a substance present in a system when that amount is too small to be measured chemically or spectroscopically, or when it cannot be quantitatively separated from other materials in the system. An example of the latter is the determination of the amount of water in the human body by injection of tritium (radioactive hydrogen).[3]

Activation analysis may be used to determine the presence of minute amounts of elements in samples of ore. The ore sample is bombarded with neutrons in a reactor, and the various radioisotopes produced are identified by their specific radiation characteristics. The "rare earth" elements, almost impossible to separate chemically, can be separated by activation analysis.[3]

Isotopes are used to study the wear and tear of friction on piston rings. A piston ring is made radioactive in a nuclear reactor. It is then fitted into the cyclinder of an engine and operated with suitable lubrication in the ordinary way. The degree of radioactivity transferred to the lubricating oil shows the extent of wear of the piston ring. Lubricating oils have been improved as a result of these studies. New companies have sprung up just to do this type of testing on railway engines and automobiles.

The efficiency of different laundry detergents and washing machines is tested by washing swatches of cloth containing radioactive dirt. A Geiger counter shows how much of the dirt was not removed.

Static electricity has always been a poorly controlled fire hazard in the printing, textile, and plastic industries until now. Radioactive sources ionize the air in contact with the statically charged surface, allowing the charge to be dissipated.

Atomic power will conserve our waning coal and oil reserves. Shortly, nuclear reactors will spring up like mushrooms all over this country. Even portable reactors are commercially available for use in hospitals to provide electricity in case of power failure.

Atomic propulsion will soon be in general use. Atomic-powered submarines are a reality. An atom-powered merchant ship, the Savannah, will be afloat in a year or so.

Aircraft designers are working frantically to whip the problem of radiation-shielding for nuclear-powered planes.[1]

Phosphorescent materials emit light under bombardment by atomic rays. This is the principle which permits the construction of markers for railway crossings, aircraft runways, planes, and ships which are self-luminous and not dependent on electrical power.[1]

In fact, there is no part of your life in which the peaceful and ubiquitous atom will not serve you in the future. If you go to a baseball game, you may even find yourself eating irradiated wieners.

Maximum Permissible Dose of Radiation

Radiation can be delivered to the body in two ways, from an outside source, or from a source present within the body. There is no such thing as total protection. In order to understand what we call "maximum permissible dose," one must be familiar with the terms currently used in radiation protection—the "roentgen," the "rad," the "RBE," and the "rem."[4]

The term "roentgen" describes only one characteristic of x-rays or γ-rays, i. e., their ionizing effect on air. It is a dose of x- or γ-rays delivered, not an absorbed dose. It is necessary to know the absorbed dose, not only of x- or γ-rays but of other kinds of radiation not measurable in roentgens, such as β-rays, neutrons, α-particles, and protons. So a new unit, the rad (radiation absorbed dose) was adopted. One rad is the absorption of 100 ergs of energy per gram of absorbing material. This applies to any kind of radiation, corpuscular, or electromagnetic. At ordinary voltages, 1 r (absorbed) equals one rad. However, some types of radiation have a much greater effect on tissue than others. For example, 1 rad of fast neutrons has 10 times more effect than 1 rad of x-rays. For this reason, the term RBE was introduced. This means the *relative biological effectiveness* of various types of radiation as compared with x-rays. Multiplying the absorbed dose in rads by the RBE of the type of radiation to which a man has been exposed, gives the total biological effect of the energy absorbed. This is expressed in rems. Rem means *roentgen equivalent man*. The RBE of x-rays is taken as 1. So if a worker is exposed to 100 millirads of x-rays during a week, his dose is 100 millirems. Suppose he is also exposed to 20 millirads of fast neutrons during the same week. The RBE of fast neutrons is 10. So his dose from neutrons is 20 times 10, or 200 millirems. This is added to the 100 millirems he obtained from x-rays, which brings his total dose to 300 millirems for the week. In the field of radiation protection, the rem is essential because it provides a unit of effect on the body, regardless of the type of radiation received.

The recommendations of the National Committee on Radiation Protection[5] are based on presently available information which cannot be regarded as final. For this reason, they insist that exposure to radiation be kept at the lowest practical level for everyone. At present, the maximum permissible dose for persons in industry is 5 rems per year, or an average of 1/10 rem per week of whole-body radiation, after the age of 18 years. However, three-fifths of this maximum yearly dose may be incurred during a single 13-week period if necessary. For the skin, the maximum permissible dose is set at 10 rems per year. This amount of exposure is not expected to cause permanent skin changes detectable by a dermatologist during the person's lifetime. Where only the hands and arms of adults are exposed for indefinite periods of time to external radiation, the maximum yearly dose can be as much as 75 rems in the skin, *provided* the resulting dose to the deeper tissues is no higher than it would be if these tissues were exposed to 75 r of ordinary x-rays in one year.[6] Let me emphasize that these maximum permissible doses are exclusive of necessary medical irradiation.

External Hazards

α-Particles from naturally occurring substances and from most isotopes are not an

external hazard, as they cannot penetrate the dead cells of the stratum corneum. They are *very dangerous* if absorbed internally. β-Rays are more penetrating than α-particles, but the energy spectrum of β-rays, and therefore, their penetrating power, varies greatly. For example, it takes 1,500 rads of β-radiation from Y^{91} on the skin surface to produce a dose of 1,200 rads in the basal layer, whereas 20,000 rads from S^{35} are required to produce the same dose in the basal layer.[7] When the skin is exposed to β-rays, it is important to know the maximum energy of the rays, as well as the amount of the dose and the half-life of the emitting substance, in order to estimate the damage.

Knowlton [8] and his associates have clearly described the symptoms of β-ray burns on the hands. Itching and tingling occur immediately or very soon after exposure, followed in a matter of hours by mild erythema and edema which persist for two or three days and then subside. The patient is symptom-free for a few more days, when erythema and edema of a severer degree develop. The resultant vesicles and bullae disappear in about three weeks, leaving the skin dry and atrophic. In hairy areas, there is permanent alopecia and loss of follicular structures. Telangiectasia and hyperkeratoses appear after varying periods of time.

The external hazards from x-rays and γ-rays attend the use of fluoroscopes, x-ray machines, radium, and γ-emitting isotopes. Exposure comes from handling or being in close proximity to the radiation source without proper shielding. When shielding is not feasible, distance is a good protection. In industry, ingenious mechanical devices allow sources to be handled by remote control. Television sets are used for remote viewing of procedures in which the operator sits behind a lead wall and manipulates large pincers which lift the "hot cargo." [1]

The practice of medicine can be considered an industry, one in which the use of ionizing radiation is common and sometimes abused through lack of knowledge or carelessness. Dermatologists are familiar with the chronic radiodermatitis on the dentist's finger and the orthopedic surgeon's hands. The fluoroscope has been considered too handy and too innocuous. For example, infants placed on the fluoroscopic table for examination receive total-body irradiation from a machine producing 40 to 50 r per minute. If such examination is repeated routinely at intervals, its dangers may greatly outweigh its benefits. The accumulated dose to the gonads may cause future mutations. Irradiation of the epiphyses may interfere with normal bone growth. Radiographic diagnostic units may give excessive doses to patients if the radiation beams are not properly collimated or if suitable filtering devices are not employed.

Shoe-fitting fluoroscopes are a totally unwarranted use of radiation. A hazard to both customer and shoe salesman, they should be outlawed everywhere, as they are in New York State. In the same category, in my opinion, is fluoroscopic crime detection, in which fluoroscopes are used to search factory employees, visitors to prisons, and people going through customs. While it may be justified in the individual case under special circumstances, such routine fluoroscoping of large numbers of the people is what I call "committing a crime to detect a crime."

In the electronic tube industry there is some hazard when large numbers of tubes are tested at voltages considerably higher than their rated values. However, the television set in your home is entirely safe. Although it operates at about 15 kv. (in the Grenz-ray range), the wall thickness of the tube provides adequate shielding. Television sets in motion picture theaters operate at about 80 kv. and can be a definite hazard to repair men making adjustments during operation. The children in the front row get less than 1 millirem per hour.[4]

Accidents in industry can always happen, due to carelessness or ignorance. At a factory, in a carefully shielded room, Co^{60} was placed on a table surrounded by metal

castings backed by photographic film. Next morning when workers opened the tightly sealed room they were surprised to find the Co^{60} on the floor. Then they found that a cat had been inadvertently locked in the room. The animal escaped into the neighboring countryside, and the word was spread around that a radioactive cat was loose, causing a panic among the villagers. The cat had been externally irradiated but had not swallowed the cobalt and was not radioactive or a menace to anyone.

Internal Hazards

Without doubt, the greatest danger attending the use of atomic energy in industry is the danger of internal absorption of radioactive substances, because, once lodged in the body, they irradiate it from within, 24 hours a day. The maximum permissible body burden of most radioisotopes is not known, and the factors determining the amount of internal radiation are many and complex.

The amount of a radioisotope internally absorbed through ingestion or inhalation depends on its solubility. In the latter case, 12% of the insoluble fraction is retained in the lungs, irradiating these critical organs.[4]

Some radioactive materials are much more dangerous to health than others because of an affinity for essential organs.[4] Ingestion of P^{32}, which seeks bone marrow, for example, is more injurious than I^{131}, which would produce comparable damage in the thyroid gland. When a high concentration of radioactive material is collected in a small organ, it is more injurious than the same amount collected in a large organ. Fifty microcuries of I^{131} can produce much more damage than fifty microcuries of Na^{24}, because the former is concentrated in a small organ, whereas the latter is distributed throughout the body.

In the case of internally absorbed radioisotopes, we must consider not only the radioactive half-life of the substance involved, but also its biological half-life, that is, the time in which the body can eliminate one-half of the substance through its own biological processes. These two factors combined give the *effective half-life*, which is defined as the time required for a specific amount of a particular radioactive substance to fall to half of its original value as a result of natural elimination and radioactive decay.[3]

The difference in average energy of emanations from one internally absorbed isotope and another is often great and must be taken into account.[4] For example, tritium (H^3) and Na^{24} are both fairly uniformly distributed throughout the body after ingestion, but Na^{24} has an average energy 450 times that of tritium. An additional factor which must be considered is the RBE of internally emitted radiations. α-Particles have 20 times the ionizing power of β- or γ-rays.

Because of these different factors, one can readily understand the difficulty of establishing the maximum permissible body burden for each of the 900 isotopes. Eventually it will be accomplished.

The cutaneous manifestations of internal diseases caused by radiation are no different, as far as we know, from those of diseases due to other causes. What we should keep in mind is that anemia, leukemia, purpura, osteogenic sarcoma, and other neoplasms can be caused by internally absorbed radiation.

Evaluation

What does this atomic industrial revolution mean to us? It means better living and greater dangers. It offers untold opportunities in research and development which will benefit all mankind—but with these benefits goes a serious health problem. We shall have a much bigger task to protect ourselves and future generations from the harmful effects of ionizing radiation.

There is no need to be afraid of the future. Let us be confident and use common sense. I do not minimize the dangers of radiation in a world where a reactor can be found "just around the corner." Neither will I be a "radiophobe," afraid of

little gremlins called "millirems." It is common sense to keep radiation exposure to everyone as low as possible, because many of the effects are unknown and may remain so for a long time. These effects may not all be harmful, but we do not know. If we have neurotic fear of the unknown, we cannot deal effectively with the health problems of this atomic age.

The AEC has been the wise father of atomic energy, fostering every peaceful use of it by education, supervision, and financial assistance. The AEC has controlled the use of isotopes by revokable licenses which require rigid adherence to safety rules. Because of compliance with AEC rules and the safe-guards instituted by management, the incidence of radiation damage in industry has lagged far behind the increased use of atomic energy.[9] Scientists see no reason why it cannot be cut to practically zero if all safe-guards are explicitly followed. The AEC's own safety record is an example for all to follow. During the last 10 years, 95% of their employees and those of their contractors received an average dose of less than 1 rem per year, and 99.4% received less than 5 rems per year.[3]

Of course we know that as atomic industry expands many unprecedented problems will arise. In spite of elaborate safeguards, there is always the human element, and accidents can happen. Furthermore, the AEC plans to relinquish part of its control to state and local authorities. There is now and will be for some time, a dire shortage of radiation health officers. Still, I firmly believe that every user of ionizing radiation can attain the same degree of safety the AEC has achieved.

The use of isotopes is so well regulated that they are not as great a hazard at the present time as x-ray machines, fluoroscopes and radium, which are not AEC controlled. Only a few states have safety laws pertaining to the use of x-rays and radium. I favor registration and even licensing of all sources of ionizing radiation, and adequate enforcement of safety regulations, in medicine, as well as in industry. We have building codes, why not an installation code for x-ray machines? We have narcotic licenses, why not a license to operate a fluoroscope or to use radium? Let me emphasize that I do not think any state should tell a physician how and when to use ionizing radiations on patients. Such regulations should only be concerned with radiation protection.

Physicians should have the scientific knowledge and the moral obligation to use radiation for diagnosis and therapy on sick people when they need it but to keep the dose as low as possible. I think if Hippocrates were alive today, he would make an addition to our oath, to-wit:

"I promise that I will use radiation for the good of my patients, and that I will, by surveys, monitoring, proper equipment, good judgment and every other means, avoid all unnecessary radiation exposure to my patients, my employees, the public, and myself."

1120 Montgomery Dr.

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Long-Term Triamcinolone Therapy of Alopecia Universalis

Case Report

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Dillaha and Rothman were the first to report the remarkable therapeutic effect of systemic cortisone on alopecia areata.[1] During the intervening seven-year period new members of the cortisone family have been shown to have a similar effect.[2] We wish to report here a striking result obtained with triamcinolone (Aristocort),* one of the most recent and potent corticosteroids yet synthesized.[3]

Report of a Case

This 18-year-old, healthy, white youth was first seen by us on Sept. 16, 1957, for the treatment of alopecia, which had been present since the age of 9 years. His hair loss had begun as two patches on the scalp, after the psychic trauma of being thrown into a swimming pool by elders who knew he could not swim. The hair loss had gradually extended to involve the entire scalp, eyebrows, and eyelashes. Terminal axillary hair had not appeared at puberty, although a very sparse pubic growth did ensue. At no time during the nine years had any appreciable hair growth been evident on the scalp or body. Treatment had been limited to topical antifungal remedies applied to the scalp during the first year after hair loss. The patient's health had been good and the history was otherwise nonrelevant. The family history was negative, eight siblings and the parents presenting no illness. Alopecia areata had not been noted by any other members of the family. Physical examination revealed a normal healthy youth with essentially complete absence of terminal body hair (Fig. 1). Nail growth was normal. A biopsy specimen of the axilla showed diminutive follicles with hair. The apocrine, as well as sebaceous, glands appeared to be entirely normal.

Treatment was initiated with 10 mg. of triamcinolone acetate orally each day. Within three weeks, hundreds of follicular papules and hair buds appeared uniformly over the entire scalp. Hair growth was obviously in progress and at five weeks was much in evidence (Fig. 2). Body hair pro-

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Department of Dermatology, University of Pennsylvania School of Medicine.

* Triamcinolone (9-α-fluoro-16-α-hydroxyprednisolone) was kindly supplied us as Aristocort by Dr. Christopher H. Demos, Lederle Laboratories, Pearl River, N. Y.

Fig. 1.—Alopecia totalis prior to treatment.

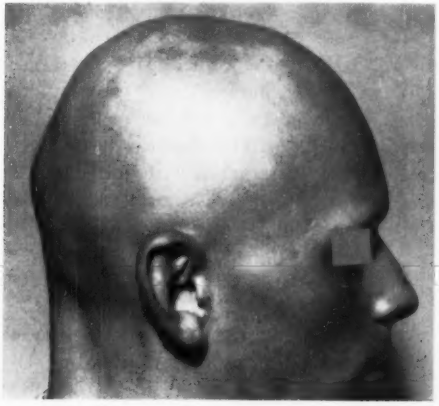

Fig. 2.—Appearance after five weeks of oral triamcinolone therapy (10 mg. per day).

Fig. 3.—Appearance after three months of therapy (8 mg. per day). Note alopecia areata area which appeared when dosage dropped below maintenance level.

Fig. 4.—Appearance after 15 months of oral triamcinolone therapy (6 mg. per day).

ceeded apace, although the eyebrows and eyelashes never acquired a full complement of hairs.

After the first month, triamcinolone dosage was reduced to 8 mg. per day. Subsequent attempts to determine the maintenance dosage revealed it to be 6 mg. per day. Whenever the dosage was dropped to 3 mg. per day, patches of alopecia areata became manifest (Fig. 3). The patient has thus been maintained on 3 to 8 mg. of triamcinolone daily for nearly a year and a half. The improvement in his appearance and psychic status has been most gratifying (Fig. 4).

Close observation has revealed no clinically discernible side-effects at this low dosage. After 15 months of continuous therapy, the following studies proved to be normal:

Complete blood cell count: Hb. 17.6 gm. %
WBC 10,000 (lymphocytes 24%, neutrophils 74, monocytes 2)
Blood sugar, fasting: 66 mg/100 ml.
Urinalysis: normal
17-Hydroxyketosteroids: 0.5 M. U.
17-Ketosteroids: 5.2 mg/24 hours
X-rays of chest and lumbosacral vertebrae: normal
Weight and blood pressure: normal

Comment

The clinical resurgence of hair growth in this patient was within three weeks, despite the long nine years of growth failure. This supports Van Scott's recent view [4] that in alopecia areata the hair roots are in a constant proliferative phase of growth but restrained from proceeding beyond this stage. Alopecia is thus a better term clinically than it is physiologically, for we can perceive that the hair is "lost" only in the clinical sense. Actually, diminutive hairs keep growing in alopecia areata.

It is significant to note that the associated pilary structures, both apocrine and sebaceous, were unaffected by the inhibitory factor. The defect is specifically centered on keratin formation.

Triamcinolone was effective only when given systemically. Topical applications (ointments, creams, lotions; 0.1%-0.25%) were without effect. This is in keeping with the experience of others with other corticosteroids.

The remarkable effectiveness of low dosage triamcinolone therapy has encouraged us to continue treatment over a long term. It is recognized, however, that this was done with careful medical surveillance and with a constant view to lowering the dosage further. Furthermore, the present study has remained investigative in nature.

Summary

A case of alopecia universalis of prepuberal onset and nine years' duration has responded well to low dosage of triamcino-

lone therapy over a period of one and one-half years. However, the steroid effect still remains a completely reversible one since reduction of the maintenance dose to below 6 mg. per day invariably has led to the appearance of alopecia areata lesions. Thus, despite prolonged administration, triamcinolone has failed to have any curative effect in this patient. This long-term investigative study indicates that one must have considerable reservation about suggesting systemic steroids in the treatment of a disease of cosmetic significance only.

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Amphotericin as a Topical Antifungal Antibiotic

A Clinical Trial

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A previously unknown Streptomyces species, isolated from a soil sample obtained at Tembladora, on the Orinoco River in South America, has been found to produce two amphoteric antifungal agents which have been named amphotericin A and amphotericin B.[1] Studies of their physical properties reveal slight differences between the infrared absorption spectra of the two materials. Crystalline amphotericin A exhibits the ultraviolet absorption curve of a conjugated tetraene similar to rimocidin or nystatin, while the absorption curve for amphotericin B is characteristic of a conjugated heptaene, and is similar to ascosin and trichomycin. These compounds also have different solubilities in various organic solvents. Although the chemical structure is not known, elementary analysis indicates that both compounds contain carbon, hydrogen, and nitrogen in similar proportion and do not contain halogen, sulfur, methoxyl, or acetyl groups.[2] Pharmacological studies reveal that the two compounds are very poorly absorbed through the gastrointestinal tract.

Amphotericin B is active in vitro against a wide variety of fungi, the most sensitive organisms being Histoplasma capsulatum, Blastomyces dermatitidis, Blastomyces brasiliensis, Microsporum audouini, and Cryptococcus neoformans.[3] Amphotericin A has a broader spectrum, inhibiting all of the test organisms in relatively low concentrations except Sporotrichum schenckii, Cephalosporium recifei, and the Nocardia species. Significant among the organisms sensitive to these two compounds are Microsporum canis, Microsporum gypseum, Trichophyton mentagrophytes, Trichophyton tonsurans, Trichophyton rubrum, Trichophyton megnini, and Trichophyton gallinae. In general, amphotericin B is more active against the yeasts and yeast-like fungi.[4]

Both the A and B forms are active parenterally or orally. In vivo amphotericin B is more active than A, even against fungi whose response to amphotericin A was better than to B in vitro.[2] Mice infected with Candida albicans, Cryptococcus neoformans, Histoplasma capsulatum, or T. mentagrophytes have responded well to amphotericin B.[5] There is no antibacterial activity.[4]

These antifungal antibiotics are relatively nontoxic. When given intraperitoneally to mice, a suspension of amphotericin B has an LD_{50} of 280 mg. per kilogram, while the sodium salt of amphotericin A has an LD_{50} of approximately 450 mg. per kilogram when given by the same route.[5]

On the basis of laboratory results, both in animals and in vitro, amphotericin should be a valuable addition to the physician's antifungal armamentarium. In fact, reports have been published indicating moderate success in the treatment of various deep fungus infections. Crounse and Lerner[6] have reported a case of systemic cryptococcosis which improved during the time the patient was receiving amphotericin B. Rubin and Furcolow have treated 10 patients with cryptococcal meningitis, of whom 8 are still living after from 2 to 14 months, and 7 have sterile spinal fluid.[7] Others have had

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The amphotericin for this study was supplied by E. R. Squibb & Sons, New York.

From the Department of Dermatology, Baylor University College of Medicine (Everett R. Seale, Chairman); Associate Professor of Dermatology (Dr. Knox).

similar encouraging results.[8-10] There was complete healing of the cutaneous lesions of North American blastomycosis in four male patients treated with intravenous amphotericin B by Harrell and Curtis.[11] Coccidioidomycosis has been benefited by systemic administration of amphotericin B.[12-14] Cases of histoplasmosis, cryptococcosis, blastomycosis, and coccidioidomycosis treated with amphotericin B, both orally and intravenously, were evaluated by Utz et al.[15] They feel the drug is useful in histoplasmosis and blastomycosis, if given intravenously, but are not impressed with the results in cryptococcosis and coccidioidomycosis.

Following discussion of his paper, "Antifungal Antibiotics in Clinical Medicine," Blank[16] commented that he had used amphotericin ointment topically in a limited study. He felt that it was ineffective in tinea capitis, tinea versicolor, and T. rubrum infections. The only other reports concerning the topical use of amphotericins in the treatment of superficial fungus infections have been concerned with moniliasis.[17] In order to determine the effectiveness of amphotericin preparations in the treatment of various superficial fungus infections, an extensive clinical investigation was undertaken. It is the purpose of this paper to report the results of this study.

Materials and Methods

One hundred fifty-four cases of superficial fungus infection were treated with amphotericin. The material used consisted of either 2% or 3% amphotericin A alone, amphotericin B alone, the two in combination with each other, or together with Spectrocin.*

In all patients included in the study, the clinical diagnosis of fungal infection was confirmed by a positive KOH preparation. The lesions were routinely cultured, but the usual percentage failed to grow. Amphotericin formulations were applied topically two to four times daily. The patients were maintained on treatment for a minimum of six weeks unless they became worse, in which case the medication was discontinued. In some instances, more than one preparation was tried.

* E. R. Squibb & Sons—Antibiotic ointment containing 2.5 mg. of neomycin and 0.25 mg. of gramicidin per gram in Plastibase.

Results

Tinea Capitis.—Of 18 cases with tinea capitis, there were 13 failures, 1 improvement, and 4 cures. There was kerion formation in 3 of the 4 cases regarded as cured; therefore, it is doubtful that the amphotericin was of value in any of the 18 cases. Eleven of these patients were infected with T. tonsurans, 3 with M. audouini, 1 with Trichophyton violaceum, and 3 with fungi of undetermined type.

Tinea Cruris.—There were six failures and one improvement in seven cases with tinea cruris. The failures included cases of T. rubrum and T. mentagrophytes. Epidermophyton floccosum was not available for inclusion in this study.

Tinea Pedis.—Thirty-one patients in this study manifested tinea pedis and failure was recorded in 25 cases, improvement in 5, and cure in 1. The only cure was a case of T. mentagrophytes. Although one additional patient improved, five other cases of T. mentagrophytes failed to respond. All cases of T. rubrum were considered to be failures.

Tinea Corporis.—Forty-five cases of tinea corporis were treated and there were 35 failures, 7 with improvement, and 3 who were regarded as cures. Cultures were positive in 22 cases and negative in 23. Of the three cures, one was M. canis and the other two were of unknown etiology. There were 16 failures, 3 with improvement, and no cures in the cases with T. rubrum.

Tinea Versicolor.—Twenty-five patients with tinea versicolor were included in this study. Seventeen were regarded as failures, eight were considered to have improved, and there were no known cures.

Moniliasis.—There were 18 cures, 8 cases with improvement, and 2 failures out of a total of 28 patients with cutaneous moniliasis. Results were often dramatic, and the disease failed to respond in only two instances. In both failures, amphotericin A was employed in combination with Spectrocin; therefore, the inclusion of antibiotics possibly contributed to the treatment failures.

Conclusions

It is readily apparent that of the 154 patients included in this study, the only favorable results were in the group with cutaneous moniliasis. Excluding the 28 patients in the latter group, there were 126 patients with various dermatomycoses. Of these, there were 96 failures (76.2%), 22 improvements (17.5%), and 8 cures (6.3%). Therefore, it is doubtful that the amphotericins will be of value in the topical treatment of routine superficial fungus infections. In contrast, the results in moniliasis were excellent. There were only two failures, and these may have been due to the inclusion of antibiotics in the formulation.

Summary

Amphotericin A and B, antifungal antibiotics derived from a new strain of Streptomycetes, have shown antifungal activity in vitro and in vivo.

Topical preparations of amphotericin A and amphotericin B were used, singly and in combination, in the treatment of 154 cases of various superficial fungus infections.

Our results indicate that the amphotericins are effective against cutaneous moniliasis but are relatively ineffective against the other superficial fungus infections of man.

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Treponemal Tests on Cerebrospinal Fluid

Experiences with the Treponema Pallidum Complement-Fixation (TPCF) and Reiter Protein Complement-Fixation (RPCF) Tests

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Previous studies employing treponemal antigens on spinal fluid have dealt for the most part with the Treponema pallidum immobilization (TPI) procedure of Nelson. Nelson and his co-workers [1] observed positive reactions in all of 33 patients with various types of central nervous system (CNS) syphilis. Interestingly enough, of 25 patients classified as latent syphilis, 6 showed TPI antibody in the spinal fluid. Durel and his co-workers [2] observed only 78% positive TPI reactions in a group of 54 spinal fluids of patients with neurosyphilis. Of 25 patients classified as latent syphilis, 7 were found to have positive TPI tests on the spinal fluid. Zellman and Lutz [3] observed a similar sensitivity of 77% in a group of 26 patients with CNS syphilis. Again, 4 of 11 patients with supposed latent syphilis had positive TPI tests on the spinal fluid. These workers conclude that in neurosyphilis the TPI antibody is uniformly present in the spinal fluid of the untreated patient and that therapy may effect its disappearance. The significance of the presence of TPI antibody in approximately 25% of the spinal fluids of patients classified as latent syphilis was not clear to these authors. They considered the possibility that the choroid plexus-meningeal barrier was more permeable to the TPI antibody than to reagin. Based on a study of 376 spinal fluids, Miller, Slatkin, and Hill [4] conclude that a positive TPI test was diagnostic of neurosyphilis, but a negative TPI test did not exclude neurosyphilis, since 14% of 100 undoubted cases of CNS syphilis, many of whom had been treated, gave negative reactions.

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Objectives

The purpose of the present study is the evaluation of the Treponema pallidum complement-fixation (TPCF) [5] and the Reiter protein complement-fixation (RPCF) [6] procedures on cerebrospinal fluid. In contrast to the technically difficult TPI procedure, these tests have the practical advantages of employing extracts of killed spirochetes in a simple complement-fixation technique adaptable to mass testing. The specific objectives of this study are as follows:

(1) The evaluation of the *specificity* of these procedures in the spinal fluids of nonsyphilitic persons.

(2) The evaluation of the *sensitivity* of these treponemal antigens in CNS syphilis as compared with the standard lipoidal complement-fixation tests.

(3) The observation and significance of the reactions with these antigens in the spinal fluids of patients clinically classified as latent syphilis.

(4) A comparative evaluation of the TPCF versus the RPCF tests.

Methods

The spinal fluids of an over-all total of 290 patients were examined in this study. Of these, 103 are omitted from critical evaluation because of incomplete historical and clinical data. The re-

TABLE 1.—*Spinal Fluids in Nonsyphilitic Controls—Data on Ninety-Six Patients in Group I* *

	R	NR	AC(NR)	ND
TPCF	0	91	5	0
RPCF	0	91	5	0
Cardio CF	0	72	0	24

* R indicates reactive; NR, nonreactive; AC(NR), anticomplementary, nonreactive on dilution; ND, not done.

maining 187 patients are classified into the following three groups:

I. Nonsyphilitic controls—96 patients.

These persons were patients at the New York University and Bellevue Hospitals, who gave negative syphilis histories, showed no physical signs of syphilis, and had negative standard serologic reactions on the blood and spinal fluid.

II. Latent syphilis—42 patients.

These persons, obtained from the same sources, as well as from private practice, gave a history of treatment for syphilis, showed no physical signs of syphilis, and had positive standard serologic tests on the blood and negative routine spinal fluid findings.

III. Central nervous system syphilis—49 patients.

These patients obtained from similar sources gave a history of syphilis and manifested either clinical evidence of CNS involvement and/or positive routine spinal fluid findings.

The TPCF antigen was obtained through the courtesy of Drs. Garson and Portnoy, of the Venereal Disease Experimental Laboratory, Chapel Hill, N. C. The RPCF antigen was obtained through Drs. de Bruijn and Bekker, National Institute of Health, Utrecht, Netherlands. Both procedures employ the ⅕ vol. Kolmer complement-fixation technique, using 1½ exact units of complement as described by Portnoy and Magnuson. Volume of spinal fluid used is 0.2 ml. undiluted. Fresh spinal fluid was not inactivated prior to testing; old spinal fluid was inactivated for 15 minutes at 56 degrees C.

In addition to the TPCF and RPCF tests the spinal fluids were routinely subjected to cell count, total protein (sulfosalicylic acid method), colloidal gold, and standard cardiolipin complement-fixation tests.

TABLE 2.—*Spinal Fluids in Latent Syphilis—Data on Forty-Two Patients in Group II* *

	R	NR	AC(NR)	QNS
TPCF	5	34	3	0
RPCF	1	25	8	8
Cardio CF	0	40	0	2

* R indicates reactive; NR, nonreactive; AC(NR), anticomplementary, nonreactive on dilution; QNS, quantity not sufficient.

Results

The results of this study can best be demonstrated by referring to Tables 1, 2, and 3.

In fairness to the proper evaluation of the RPCF test in CNS spinal fluids the following data should be mentioned. Of the six spinal fluids recorded as nonreactive, two were also nonreactive with the TPCF and the standard cardiolipin complement-fixation tests. The remaining four, which were all reactive with the TPCF and standard cardiolipin complement-fixation tests, were tested one and one-half to four years later than the standard complement-fixation test on the same specimen of spinal fluid. One of these specimens previously reactive with the TPCF became nonreactive with this test when tested simultaneously with the RPCF test one and one-half years later. These facts are significant, since we have observed a considerable tendency toward nonreactivity in specimens stored for any length of time in the deep freeze.

Comment

In CNS syphilis, 91% of the spinal fluids were reactive with the TPCF test and 85% with the RPCF procedure under the conditions of this study. It should be noted that all of the nonreactive spinal fluids were obtained from patients with *treated* CNS syphilis. There were only two patients nonreactive with the TPCF who were reactive with the standard cardiolipin complement-fixation procedure. Only one was nonreactive with the RPCF and reactive with the standard cardiolipin complement-fixation

TABLE 3.—*Spinal Fluids in CNS Syphilis—Data on Forty-Nine Patients in Group III* *

	R	NR	AC(NR)	AC	QNS	ND
TPCF	43	4	0	2	0	0
RPCF	34	6	3	2	4	0
Cardio CF	36	13	0	0	0	0
TPI	0	12	0	0	0	37

* R indicates reactive; NR, nonreactive; AC(NR), anticomplementary, nonreactive on dilution; AC, anticomplementary; QNS, quantity not sufficient; ND, not done.

test. It is striking to observe that 12 patients with central nervous system syphilis were nonreactive with the TPI test, yet all reacted with the TPCF procedure. Moreover, all but one reacted with the RPCF test on the spinal fluid. Of these 12 patients, 7 showed positive reactions with the standard cardiolipin complement-fixation test.

It would appear that the decreasing order of sensitivity of the procedures performed in this study are TPCF, RPCF, cardiolipin complement fixation (CCF), and TPI.

There was no correlation whatsoever between the reactivity with the treponemal tests and the reactivity of the CNS process as measured by clinical and/or spinal fluid (Dattner-Thomas) criteria. It would appear that a positive reaction with these tests indicates past or present involvement of the central nervous system. A negative treponemal test does not rule out CNS involvement, since antisyphilitic therapy may reverse the reaction.

The specificity of these procedures is 100%, there being no reactivity in a group of 96 nonsyphilitic controls. Adequate comparison of the sensitivity of the RPCF as compared with the standard cardiolipin complement-fixation test is not justified under the conditions of this study.

In the group of 42 patients clinically classified as latent syphilis, the finding of 13% reactive with the TPCF test on the spinal fluid corresponds to similar studies employing the TPI technique. In our opinion these persons should be reclassified as cases of asymtomatic neurosyphilis. Furthermore, it would appear that the criteria of the diagnosis of latency should be revised to include negative reactions with the more specific and more sensitive tests.

Summary and Conclusions

The Treponema pallidum complement-fixation (TPCF) and Reiter protein complement-fixation (RPCF) tests were performed on the spinal fluids of 290 patients, of which 187 are evaluated in this study.

All 96 nonsyphilitic normal controls were nonreactive, indicating 100% specificity.

Of 42 supposed latent syphilis spinal fluids, 13% were reactive with the TPCF and 4% with the RPCF tests.

Of 41 central nervous system (CNS) spinal fluids, 91% were reactive with the TPCF test, 85% of 40 such spinal fluids were reactive with the RPCF test.

A positive TPCF and/or RPCF test indicates past or present CNS involvement.

There is no correlation between the reactivity of these tests and activity of the CNS process.

The concept of latency should be expanded to include negative reactions with the treponemal tests.

These procedures should be performed on fresh spinal fluid specimens, since storage in the deep freeze can render previously reactive specimens nonreactive.

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Pemphigus Vulgaris and Diabetes Mellitus

A Case Report

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Diabetes mellitus complicated by pemphigus vulgaris, or the reverse, has not been reported. The usual fatal course of pemphigus has been changed in recent years by the systemic therapy with cortisone and its related substances.

Carbohydrate metabolism is affected by the use of adrenocortical and related therapy. Glycogen stores are increased. Normal subjects may show hyperglycemia, glycosuria, and a lowered tolerance to carbohydrates. In persons with diabetes, when most cortisone substances are used a decreased sensitivity to insulin is shown which is reversed when the cortisone substances are stopped.

Our patient showed the classical symptoms of pemphigus vulgaris, such as a generalized bullous skin eruption first starting under the breasts and in the axillae, then developing on the abdomen and later extending to the extremities. The bullae were filled with a clear exudate which later became turbid or purulent. Some of the bullae developed on normal skin and later the surrounding skin might become erythematous. All stages of bullae development to their rupture, raw surface, and crust formation, as well as erythematous plaques and hemorrhagic bases, were seen. There were only a few mucous membrane lesions.

The histopathologic examination showed a picture which could be compatible with pemphigus.

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Torrance Memorial Hospital.

Report of a Case

A 64-year-old Spanish-American woman was admitted to the hospital Jan. 23, 1959, and discharged Feb. 15, 1959. She gave no history of a previous skin condition. She showed symptoms of a lung congestion with a low-grade fever. The urinalysis showed acetone and sugar. The blood sugar varied from 131 to 208 mg. per 100 cc. on different days of hospitalization. A blood cell count showed 18% eosinophils. A metisteroid was given but as the dosage was increased, the necessary insulin dosage had to be increased from 20 to 50 units daily. The skin condition was little, if any, improved. The diabetic condition was not regulated. With the use of dexamethasone (Deronil) larger doses were possible, improvement in the skin and general well being was immediate, and in a few days the lesions cleared rapidly. The diabetic condition was easily controlled. The patient was discharged ambulatory.

Summary

A case of pemphigus vulgaris and diabetes mellitus was treated successfully with dexamethasone (Deronil),* a new variation of prednisolone, with no difficulty in the control of the diabetic condition.

302 Times Building (2).

* Schering Corporation, Bloomfield, N. J.

Fig. 1.—Bullae on normal skin. Old ruptured bullae with hemorrhagic bases are seen. The histopathology showed acantholytic bullae where they are formed above the basal layer.

Fig. 2.—All stages and forms of skin change are seen in this picture.

The *P*-Toluene Sulfonic Acid Test for Systemic Lupus Erythematosus

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Because of the time and skill involved in obtaining a positive L.E. preparation, a simple, clinically adaptable macroscopic precipitation test for systemic lupus erythematosus has been proposed. This has received considerable interest,[1-4] although no mention of it has been made as yet in the dermatologic literature. In brief, the test is done by the addition of a 12% solution of *p*-toluene sulfonic acid in glacial acetic acid to serum or plasma. The resultant precipitate indicates a positive test. At present, this precipitant has not been identified.

Recent reports indicate that, although the test is of interest, contrary to the original work, it has no value for the specific diagnosis of lupus erythematosus. It does not help to differentiate systemic lupus erythematosus from the related disorders. Dubois[2] has said: "It is of value only when positive, and then it indicates the presence of hyperglobulinemia." In an effort to evaluate this test for a dermatological service, we have examined the sera of 117 patients, including 6 cases of systemic lupus erythematosus and 41 patients with other related disorders. In most instances we did serum proteins (Table).

From the accompanying Table it can be seen that positive *p*-toluene sulfonic acid tests were obtained in some cases of lupus erythematosus, rheumatoid arthritis, sarcoidosis, rheumatic fever, erythema multiforme, herpes zoster, hepatitis, and leg ulcer. Furthermore, in nearly every case where the test was positive, hyperglobulinemia also was present. Other authors (ref-

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p-Toluene Sulfonic Acid Tests

Case No.	Disease	Total Proteins	Albumin	Globulin
	A. Positive Tests			
1	Disseminated L. E. (acute)	7.3	4.0	3.3
2	Disseminated L. E. (acute)	6.2	2.9	3.3
3	Discoid L. E.	7.5	2.3	5.2
4	Rheumatoid arthritis	7.3	2.2	5.1
5	Rheumatoid arthritis			
6	Rheumatoid arthritis			
7	Suspected L. E.	7.1	3.1	4.0
8	Rheumatic fever			
9	Sarcoidosis	7.1	2.5	4.5
10	Sarcoidosis			
11	Sarcoidosis			
12	Sarcoidosis			
13	Erythema multiforme			
14	Herpes zoster	7.7	3.3	4.4
15	Hepatitis	8.4	2.5	5.9
16	Stasis leg ulcer	10.0	3.6	6.4
	B. Negative Tests			
1	Disseminated L. E. (acute)	6.5	4.0	2.5
2	Disseminated L. E. (acute)			
3	Disseminated L. E. (subacute)	6.9	4.4	2.5
4	Disseminated L. E. (subacute)	4.4	3.1	1.3
5	Discoid L. E.	7.3	4.2	3.1
6	Discoid L. E.	6.4	3.3	3.1
7	Rheumatoid arthritis			
8	Rheumatoid arthritis	7.3	2.2	5.1
9	Rheumatoid arthritis			
10	Rheumatoid arthritis	7.1	4.2	2.9
11	Rheumatoid arthritis			
12	Rheumatoid arthritis			
13	Rheumatoid arthritis			
14	Rheumatoid arthritis			
15	Rheumatoid arthritis	7.4	5.0	2.9
16	Rheumatoid arthritis			
17	Rheumatoid arthritis			
18	Rheumatoid arthritis			
19	Rheumatoid arthritis			
20	Rheumatoid arthritis			
21	Rheumatoid arthritis			
22	Dermatomyositis	6.7	3.3	3.4
23	Dermatomyositis			
24	Dermatomyositis			
25	Rheumatic fever			
26	Rheumatic fever			
27	Rheumatic fever	6.9	3.2	3.7
28	Rheumatic fever	8.4	4.2	4.2
29	Rheumatic fever	6.9	3.2	3.7
30	Suspected L. E.	6.5	3.7	2.8
31	Rheumatic fever	7.3	2.2	5.1
32	Rheumatic fever	7.7	3.1	4.6
33	Rheumatic fever	3.7	1.8	1.5
34	Rheumatic fever			
35	Rheumatic fever	6.9	3.5	3.4

p-*Toluene Sulfonic Acid Tests*—Continued

Case No	Disease	Total Proteins	Albumin	Globulin
36	Rheumatic fever			
37	Rheumatic fever			
38	Rheumatic fever			
39	Rheumatic fever	7.7	4.0	3.7
40	Rheumatic fever			
41	Rheumatic fever			
42	Nephrosis	4.7	1.9	2.8
43	Nephrosis	3.4	0.9	2.5
44	Pemphigus vulgaris			
45	Pemphigus vulgaris			
46	Pemphigus vulgaris			
47	Pemphigus vulgaris			
48	Infectious eczematoid dermatitis			
49	Infectious eczematoid dermatitis	7.5	4.6	2.9
50	Infectious eczematoid dermatitis	6.7	3.7	3.0
51	Contact dermatitis	6.7	4.3	2.4
52	Contact dermatitis			
53	Stasis dermatitis			
54	Exfoliative dermatitis			
55	Nummular dermatitis			
56	Psoriasis	7.5	4.3	3.2
57	Seborrheic dermatitis			
58	Pyoderma			
59	Lichen planus			
60	Vasomotor reaction	7.9	4.4	3.5
61	Congestive heart failure	6.9	3.4	3.5
62	Lymphadenosis benigna cutis			
63	Tinea pedis			
64	Dyshidrosis			
65	Convulsions etiology?			
66	Arthritis, etiology?			
67	Lymphopathia venereum	8.4	4.0	4.4
68	Neurosyphilis			
69	Erythema multiforme			
70	Cirrhosis	3.8	1.5	2.3
71	Gout			
72	Bronchopneumonia	7.5	3.8	3.7
73	Paget's disease (bone)	7.9	4.0	3.9
74 - 117	Normal (approximately 43)			

erences [2,6]) have shown that this is not even a specific test for hyperglobulinemia, since half of their cases with hyperglobulinemia gave negative tests. One third of our such cases gave negative results.

Conclusion

The *p*-toluene sulfonic acid precipitation test is of no value as a laboratory aid in the diagnosis of systemic lupus erythematosus or of a hyperglobulinemia.

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Pathological Changes Associated with Aluminum and Zirconium Compounds

An Experimental Study of Skin Pathology Following the Application of Aluminum Chlorohydroxide, Aluminum Sulfate, Sodium Aluminum Lactate, and Zirconium Tetraisopropoxide

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In an earlier study performed in this laboratory, it was demonstrated that sodium zirconium lactate, which was used in commercial deodorants, would uniformly produce inflammatory changes in the skin of rabbits with ultimate granuloma formation.[1] This study has now been extended to include observations on two other chemicals used in commercial deodorants—aluminum chlorohydroxide and aluminum sulfate—and two chemicals with deodorant possibilities—sodium aluminum lactate and zirconium tetraisopropoxide.

Methods and Materials

Albino rabbits approximately 4 months of age and weighing 1,500 to 2,000 gm. were used in these experiments. The test chemicals were administered by three basic routes as follows: subcutaneous (0.5 ml. of the chemical in solution), using the skin of the rabbit's back from which the hair had been removed by electric clippers; intracutaneous (0.1 ml. of the test solution), using the skin on the inner aspect of the rabbit's ear, which is usually covered with sebum and sparse hair and is somewhat analogous to human skin, and percutaneous, using cotton pads saturated with the test solution and held to the skin of the rabbit's ear by Scotch tape. The three basic routes of administration were modified further by being applied to intact undamaged skin and to skin which had been deliberately damaged with superficial lacerations made by a straight back razor and finally by repeated applications.

The reactions from these injections were measured after 24 and 48 hours, 1, 2, 3, and 4 weeks. The diameter of the inflammatory infiltrate was determined and used as an index of the severity of the reaction. Biopsy specimens were taken at intervals to correlate the gross and microscopic findings.

The solutions tested and their strengths are listed below. The concentration of aluminum chlorohydroxide complex and aluminum sulfate found in commercial deodorants was used as a guide for the concentration of these chemicals used in this study.

1. Aluminum chlorohydroxide complex, 22%
2. Aluminum sulfate, 17%
3. Sodium aluminum trilactate (3.34 gm. Al_2O_3 per 100 gm. solution)
4. Aluminum chlorohydroxide complex, 22%
   Hexachlorophene (1 gm. per 100 ml. H_2O)
5. Aluminum sulfate, 17%
   Hexachlorophene (1 gm. per 100 ml. H_2O)
6. Sodium aluminum trilactate (3.34 gm. Al_2O_3 per 100 gm. solution)
   Hexachlorophene (1 gm. per 100 ml. H_2O)
7. Zirconium tetraisopropoxide, 20%
8. Zirconium tetraisopropoxide, 20%
   Hexachlorophene (1 gm. per 100 ml. H_2O)
9. Hexachlorophene (2 gm. per 100 ml. H_2O)

Results

Aluminum Chlorohydroxide Complex, 22% (Table 1).—The subcutaneous injection of 110 mg. of aluminum chlorohydroxide complex into animals not previously exposed to the chemical caused a 1 cm. area of redness after 24 hours on both the injured and uninjured sides; after 48 hours, redness and some crusting were present on the injured side, but no visible lesion was present on the uninjured side. An abscess developed at the site of injection on the uninjured side after two weeks which did not heal over a seven-week period of ob-

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TABLE 1.—*Aluminum Chlorohydroxide Complex, 22%*

Dose Mg.	Route	Skin	Dose No.	Day 1st	2d	7th	14th	Further	Gran.
110	S. C.	Intact	1	Red 1 cm.	0		Abscess	Not healed 7 wk.	+
110	S. C.	Injured	1	Red 1 cm.	Red with crust		0		0
110	S. C.	Repeat	2	Red & induration	Same	Depressed gray center			+
22	I. C.	Intact	1	Red	0	0	0		0
22	I. C.	Injured	1	Red	Red with crust	0	0		0
22	I. C.	Repeat	2	Red & induration	Depressed gray center	0	0		0
	Percut.	Intact	1	Sl. red	0	0	0		0
	Percut.	Injured	1	Sl. red	0	0	0		0
	Percut.	Repeat	2	Sl. red	0	0	0		0
				Aluminum Chlorohydroxide Complex, 22%, Plus Hexachlorophene					
Al. 55									
Hex. 2.5	S. C.	Intact	1	Red	Red	0	0		0
Hex. 2.5	S. C.	Injured	1	Red	Red	0	0		0
Hex. 2.5	S. C.	Repeat	2	Red	Ulcer	Ulcer	Ulcer	Ulcer present at 3 wk.	0
Al. 11									
Hex. 0.5	I. C.	Intact	1	Red	0	0	0		0
Hex. 0.5	I. C.	Injured	1	Red	Red	0	0		0
Hex. 0.5	I. C.	Repeat	2	Red & induration					0
	Percut.	Intact	1	Red	Red	0	0		0
	Percut.	Injured	1	Red	Red	0	0		0
	Percut.	Repeat	2	Red	Red	0	0		0

servation. Biopsy of this lesion after seven weeks revealed a central necrotic zone with a thick fibrous wall. Despite the absence of gross changes in the skin, a few granulomas were found in the deep dermis at a distance from the abscess. These consisted of nonencapsulated masses of giant cells, histiocytes, and some acute inflammatory cells. The giant cells and histiocytes contained a granular material (aluminum?) which was not related to the dermal appendages (Fig. 1).

Aluminum chlorohydroxide, 110 mg., was again injected subcutaneously seven weeks

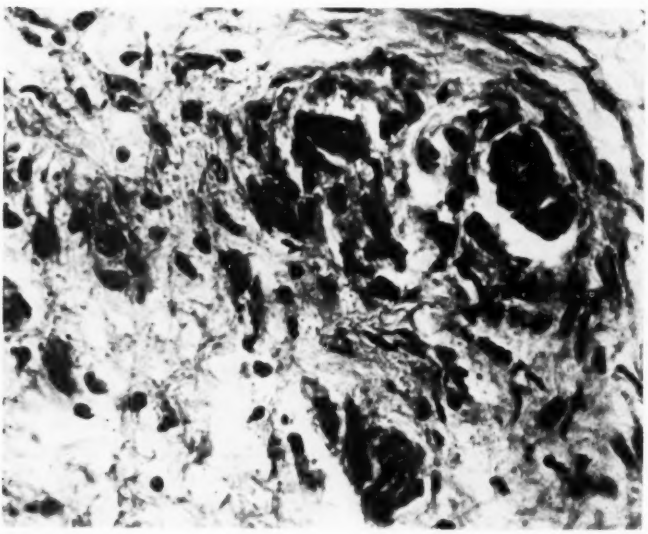


Fig. 1.—Granuloma in the subcutaneous tissue seven weeks after injection of aluminum chlorohydroxide complex, 22%.

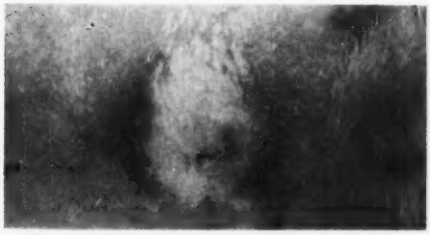


Fig. 2.—Central indurated area 24 hours after the repeat subcutaneous injection of aluminum chlorohydroxide.

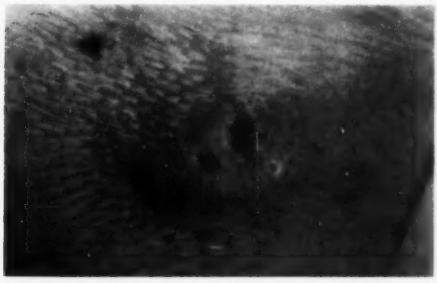


Fig. 3.—Nodule in the ear one month after intracutaneous injection of aluminum chlorohydroxide combined with hexachlorophene.

after the original experiment. There was a 1 cm. halo of redness surrounding a 1.5 cm. area of grayish induration after 24 hours (Fig. 2). The redness faded over a period of nine days, leaving the depressed gray center. Diffuse dermal edema and multiple granulomas were shown by biopsy of this tissue. The latter were nonencapsulated and composed predominantly of histiocytes with several bizarre-shaped, multinucleated giant cells. There was no constant relationship to the skin appendages, and, in general, these lesions were histiologically similar to those resulting from a single subcutaneous injection of aluminum chlorohydroxide.

Intracutaneous injection of 22 mg. of aluminum chlorohydroxide resulted in redness at the site of injection 24 hours later; after 48 hours, there was redness with slight crusting on the injured side, but no lesions could be seen on the uninjured side. Seven days later, both areas were grossly normal. Repeat intracutaneous injections seven weeks after the original injection produced redness and induration after 24 hours; this was replaced by a grayish lesion with a depressed center after 48 hours. No lesions could be seen after seven days.

Percutaneous application of aluminum chlorohydroxide caused slight redness at sites of application, which faded within 24 hours.

The subcutaneous injection of 55 mg. and the intracutaneous injection of 11 mg. of aluminum chlorohydroxide, combined with 2.5 and 0.5 mg. of hexachlorophene, respectively, failed to show reactions which were either grossly or microscopically as severe as those seen after the injection of larger amounts of aluminum chlorohydroxide alone. After the intracutaneous injection of this combination, a firm 1 cm. nodule developed which persisted for longer than one month (Fig. 3). Biopsy revealed it to be an epidermal-type inclusion cyst with foreign-body giant-cell reaction which was probably related to the trauma of injection rather than the chemicals used.

A repeat injection of this combination eight weeks after the initial injection resulted in a raised red area at the injection site after 24 hours. The area enlarged rapidly and after 48 hours measured 4×2 cm. in diameter; beginning ulceration could be seen. One week later, this lesion had gone on to frank ulceration which slowly regressed over a three-week period. Biopsy specimen showed nonspecific acute and chronic inflammation without evidence of granuloma formation.

Percutaneous application of this aluminum chlorohydroxide-hexachlorophene mixture produced only a moderate degree of edema and redness which disappeared in three days. The animals did scratch at the area, and some of this reaction may have been simple trauma.

Aluminum Sulfate, 17% (Table 2).—Areas of redness (1 cm.) developed 24 hours after the subcutaneous injection of 85 mg. of aluminum sulfate into intact and injured

TABLE 2.—*Aluminum Sulfate, 17%*

Dose Mg.	Route	Skin	Dose No.	Day 1st	2d	7th	14th	Further	Gran.
85	S. C.	Intact	1	Red 1 cm.	Depressed gray center	Fading	0		0
85	S. C.	Injured	1	Red 1 cm.	Depressed gray center	Same	Ulcer	Healed 3 wk.	0
85	S. C.	Repeat	2	Red & induration	Same	Fading		Healed (no ulcer)	0
17	I. C.	Intact	1	Red	Depressed gray center	Fading	0		0
17	I. C.	Injured	1	Red	Depressed gray center	Same	Ulcer *	Healed 3 wk.	0
17	I. C.	Repeat	2	Red & induration	Increased			Healed (no ulcer)	0
	Percut.	Intact	1	Red	Red	0			0
	Percut.	Injured	1	Red	Red	0			0
	Percut.	Repeat	2	Red	Red	0			0
				Aluminum Sulfate, 17%, Plus Hexachlorophene					
Al. 42.5									
Hex. 2.5	S. C.	Intact	1	Red	Ulcer	Ulcer	Ulcer	Healed 30 days	0
Hex. 2.5	S. C.	Injured	1	Red	Ulcer	Ulcer	Ulcer	Ulcer present at 3 wk.	0
Hex. 2.5	S. C.	Repeat	2	Red & induration	Ulcer	Ulcer	Ulcer	Healed 4 wk.	0
Al. 8.5									
Hex. 0.5	I. C.	Intact	1	Red	Depressed gray center			Fading 3 wk.	0
Hex. 0.5	I. C.	Injured	1	Red	Ulcer	Ulcer	Ulcer		0
Hex. 0.5	I. C.	Repeat	2	Red	Red				0
	Percut.	Intact	1	Sl. red	0				0
	Percut.	Injured	1	Red	0				0
	Percut.	Repeat	2	Red	0				0

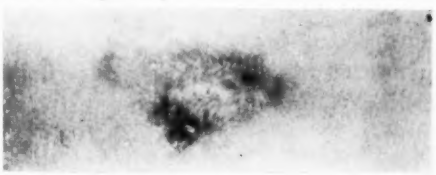
* Rabbit ear perforated.

Fig. 4.—Subcutaneous tissue reactions 48 hours after the injection of aluminum sulfate. The previously injured area is on the right side.

skin. During the second 24 hours, the central portion of this area became depressed and gray in color with the gross reaction being more severe in the previously injured area (Fig. 4). The tissue reaction on the uninjured side gradually faded over a period of seven days, but the reaction on the injured side went on to frank ulceration which progressively healed over a period of three weeks. Biopsy specimen after 48 hours revealed diffuse acute inflammatory reaction with no granuloma formation. Another biopsy specimen after three weeks revealed a chronic inflammatory reaction with a few pockets of acute inflammatory cells. Rare collections of histiocytes were present, but there were no well-formed granulomas.

Repeat subcutaneous injections of 85 mg. of aluminum sulfate were performed eight weeks after the initial injections. There was a 1.5 cm. indurated gray area surrounded by a 1 cm. red halo at the site of injection 24 hours later. The area of gross inflammatory change reached its maximum after

Fig. 5. Subcutaneous tissue reaction 48 hours after the repeat injection of aluminum sulfate.



48 hours (Fig. 5). Microscopic examination of this tissue after seven days revealed evidence of acute and chronic inflammation with a few histiocytes containing a coarse granular material (aluminum?).

Percutaneous application of a 17% solution of aluminum sulfate produced transient redness and heat during the first 48 hours which gradually disappeared during the second 48 hours.

The subcutaneous injection of 42.5 mg. and the intracutaneous injection of 8.5 mg. of aluminum sulfate, combined with hexachlorophene, 2.5 mg. and 0.5 mg., respectively, resulted in 1.5 cm. areas of redness at all injection sites after 24 hours. Ulceration developed in the previously injured site after 48 hours (Fig. 6). One week after injection, the ulcer measured 1 cm. in diameter and the histological pat-

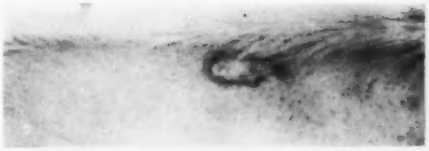


Fig. 6.—Intracutaneous reaction 48 hours after the injection of aluminum sulfate combined with hexachlorophene.

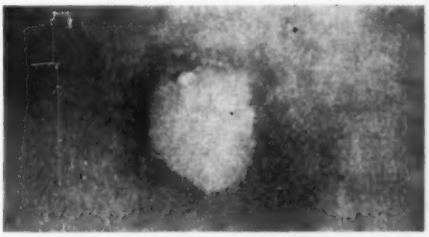


Fig. 7.—Central indurated area 48 hours after the repeat injection of the aluminum sulfate-hexachlorophene mixture.

TABLE 3.—*Sodium Aluminum Trilactate (3.34 Gm. Al_2O_3 per 100 Gm. Solution)*

Dose Mg.	Route	Skin	Dose No.	Day 1st	2d	7th	14th	Further	Gran.
16.7 *	S. C.	Intact	1	Red	Depressed gray center	Abscess	Ulcer	Persisted beyond 7 wk.	0
16.7	S. C.	Injured	1	Red	Depressed gray center	Abscess	Ulcer	Persisted beyond 7 wk.	0
16.7	S. C.	Repeat	2	Red & induration	Same	Ulcer	Ulcer	Ulcer present at 4 wk.	0
3.4	I. C.	Intact	1	Red	Depressed gray center	Abscess	Ulcer	Present at 7 wk.	0
3.4	I. C.	Injured	1	Red	Depressed gray center	Abscess	Ulcer	Present at 7 wk.	0
3.4	I. C.	Repeat	2	Red & induration	Same			Ulcer present at 4 wk.	0
	Percut.	Intact	1	0	0				
	Percut.	Injured	1	0	0				0
	Percut.	Repeat	2	0	0				0
				Sodium Aluminum Trilactate (as above) Plus Hexachlorophene					
Al. 8.35									
Hex. 2.5	S. C.	Intact	1	Red	Red	Ulcer	Ulcer	Healed 3 wk.	0
Hex. 2.5	S. C.	Injured	1	Red	Red	Ulcer	Ulcer	Healed 3 wk.	0
Hex. 2.5	S. C.	Repeat	2	Red & induration	Ulcer	Ulcer	Ulcer	Healed 4 wk.	0
Al. 1.7									
Hex. 0.5	I. C.	Intact	1	Red	Depressed gray center	Abscess	Ulcer	Ulcer beyond 7 wk.	0
Hex. 0.5	I. C.	Injured	1	Red	Ulcer	Ulcer	Ulcer	Healed 3 wk.	0
Hex. 0.5	I. C.	Repeat	2	Red	Ulcer	Ulcer	Ulcer	Healed 3 wk.	0
	Percut.	Intact	1	0	0				0
	Precut.	Injured	1	0	0				0
	Percut.	Repeat	2	0	0				0

* Solution standardized by the aluminum oxide content.

Fig. 8.—Subcutaneous tissue reactions 48 hours after the injection of sodium trilactate. The previously injured area is on the right.

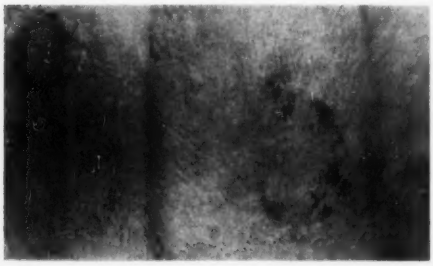


Fig. 9.—Intracutaneous reactions three weeks after the injection of sodium aluminum trilactate. The previously injured area is on the right.

tern showed nonspecific acute and chronic inflammatory change. An ulcer developed after one week at one of the uninjured sites which microscopically revealed nonspecific inflammatory changes with a few foreign-body type giant cells. These ulcerated areas healed very slowly over a period of four weeks.

The aluminum sulfate-hexachlorophene mixture was again injected subcutaneously eight weeks later. A 0.8 cm. grayish indurated area with a 0.3 cm. red halo developed 24 hours later. After 48 hours, the grayish indurated area increased in size to 1.1 cm. with superficial ulceration (Fig. 7). The biopsy performed two weeks after injection showed scattered acute and chronic inflammatory cells with no evidence of granuloma formation. Healing was complete after four weeks.

Percutaneous application of this combination produced slight edema and redness after 24 hours with complete disappearance after 48 hours.

Sodium Aluminum Trilactate (Table 3). This compound is standardized by its Al_2O_3 content (3.34 gm. %) because the sodium is not present in stoichiometric amounts. The subcutaneous injection of 16.7 mg. and the intracutaneous injection of 3.4 mg. of sodium aluminum trilactate into injured and intact skin resulted in 1 to 1.5 cm. areas of erythema after 24 hours. In 48 hours, all lesions had developed a grayish depressed center with a red crusted halo (Fig. 8). These lesions, after one week, were histologically typical of early abscess formation. Black-based ulcers with considerable induration were present three weeks after the experiment began (Figs. 9 and 10). Biopsy specimens of these revealed the cellular reaction associated with acute and chronic inflammation. After four weeks, there was essentially no change in the clinical picture, but biopsy specimens revealed large sheets of granular histiocytes.

Sodium aluminum trilactate, 16.7 mg., was again injected subcutaneously seven weeks after the initial experiment. A 2 cm. area of induration with a red halo developed at the injection site after 24 hours and the area ulcerated promptly. After 72 hours, a large area of secondary infection occurred near the ulcer, which possibly resulted from

Fig. 10.—Subcutaneous reaction three weeks after the injection of sodium aluminum trilactate. The previously injured area is on the right.

Fig. 11.—Indurated area 72 hours after the repeat injection of sodium aluminum trilactate. The large ulcer on the right is secondary to scratching.

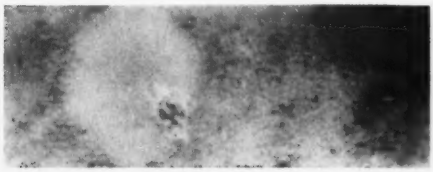


Fig. 12.—Ulceration after the repeat injection of sodium aluminum trilactate-hexachlorophene mixture into the subcutaneous tissue.

scratching (Fig. 11). Biopsy specimens after three weeks revealed acute and chronic inflammatory changes without granuloma formation.

The above experiments were repeated by injecting 8.35 mg. of sodium aluminum trilactate combined with 2.5 mg. of hexachlorophene subcutaneously and 1.7 mg. of the aluminum compound and 0.5 mg. of hexachlorophene intracutaneously. Erythema developed in 24 hours and ulceration in 48 hours after these injections. All areas but one were healed after three weeks. Histologically, these lesions were characteristic of nonspecific acute and chronic inflammation without granuloma formation.

Repeat injections of the sodium aluminum trilactate and hexachlorophene mixture seven weeks after the original experiment produced lesions with gray depressed centers surrounded by a red halo. Ulceration developed after 72 hours (Fig. 12). Two weeks after injection, the ulcer was decreasing in size; biopsy specimens revealed nonspecific inflammatory changes. Healing was complete after four weeks.

Percutaneous application of sodium aluminum trilactate alone or in combination with hexachlorophene failed to produce any gross evidence of inflammation.

Zirconium Tetraisopropoxide.—The subcutaneous injection of 100 mg. and the intracutaneous injection of 10 mg. of zirconium tetraisopropoxide produced slight redness after 24 hours, which faded during the second 24 hours.

Injection of this zirconium compound seven weeks after the original tests produced a small area of redness which disappeared gradually over the subsequent 48 hours (Fig. 13).

The subcutaneous injection of 50 mg. of zirconium tetraisopropoxide and 2.5 mg. of hexachlorophene and the intracutaneous injection of 5 mg. of the zirconium compound and 0.5 mg. of hexachlorophene resulted in the development of erythema at all injection

TABLE 4.—*Zirconium Tetraisopropoxide, 20%*

Dose Mg.	Route	Skin	Dose No.	Day 1st	2d	7th	14th	Further	Gran.
100	S. C.	Intact	1	Red	0	0	0		0
100	S. C.	Injured	1	Red	Red	0	0		0
100	S. C.	Repeat	2	Sl. red	0	0			0
10	I. C.	Intact	1	0	0				0
10	I. C.	Injured	1	Red	Red	0	0		
10	I. C.	Repeat	2	Red	0	0			0
	Percut.	Intact	1	0	0				0
	Percut.	Injured	1	0	0				0
	Percut.	Repeat	2	0	0				0
				Zirconium Tetraisopropoxide, 20%, Plus Hexachlorophene, 50%					
Zir. 50									
Hex. 2.5	S. C.	Intact	1	Red	Red	0	0		0
Hex. 2.5	S. C.	Injured	1	Red	Red		Ulcer	Healed at 5 wk.	0
Hex. 2.5	S. C.	Repeat	2	Red	0	0			0
Zir. 5									
Hex. 0.5	I. C.	Intact	1	Red	0				0
Hex. 0.5	I. C.	Injured	1	Red			Ulcer	Healed at 5 wk.	0
Hex. 0.5	I. C.	Repeat	2	Red	0				0
	Percut.	Intact	1	0	0				0
	Percut.	Injured	1	0	0				0
	Percut.	Repeat	2	0	0				0

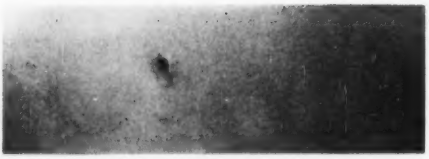


Fig. 13.—Erythematous area after the repeat subcutaneous injection of zirconium tetraisopropoxide. This type of reaction was noted at 24 hours.

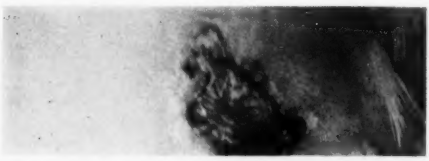


Fig. 14.—Chronic ulcer three weeks after the injection of the zirconium-hexachlorophene mixture.

sites after 24 hours. Ulceration requiring five weeks for healing developed at the previously injured sites during the two-week period after injection (Fig. 14). Histologically, these ulcerations revealed nonspecific inflammatory reaction with no evidence of granuloma formation.

A repeat injection of this combination seven weeks after the original experiment caused slight redness to develop after twenty-four hours, which then rapidly faded without ulceration.

Percutaneous application of zirconium tetraisopropoxide alone or in combination with hexachlorophene failed to produce any evidence of pathology.

Summary

Several experiments making use of albino rabbits as test animals have been performed to study the tissue reactions to subcutaneous and intracutaneous injections and to percutaneous application of a variety of aluminum salts and zirconium tetraisopropoxide.

Acute inflammatory reactions with tissue necrosis and ulceration were noted in association with the subcutaneous and intracutaneous injection of the aluminum compounds. There was a more marked reaction at the injection sites in areas that had been previously injured. Repeated injections, either subcutaneously or intracutaneously, resulted in the same type of cutaneous ulcers, but these were not felt to be more severe than those following the original injections. Granulomas were seen only after the subcutaneous injection of aluminum chlorohydroxide complex. All lesions went on to normal, although delayed, healing. The percutaneous application of these chemical compounds failed to produce any significant lesions.

The zirconium compound produced significant subcutaneous and intracutaneous reactions only when combined with hexachlorophene. Ulcerative lesions were produced only in areas in which there had been previous injury. Percutaneous application of the zirconium-hexachlorophene mixture produced no changes.

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Clinical Features of Contact Dermatitis Due to Neomycin

Report of Cases

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In general, allergic cutaneous sensitivity reactions, after the topical application of neomycin, are considered to be rare. Baer and Ludwig [1] reported the first case of contact sensitivity to neomycin. Sulzberger and Baer [2] stated that they occasionally saw contact sensitivity to this antibiotic. Epstein [3,4] was the first to report a series of patients with neomycin sensitivity. However, his patients did not present the typical and easily recognizable picture of contact dermatitis. In the majority of cases which he reported, for the most part, the diagnosis depended upon a heightened index of suspicion, rather than on the easy recognition of the classical clinical features of an acute contact dermatitis. In this series, Epstein was of the opinion that he proved the etiological role of neomycin by the demonstration of positive intradermal tests to the antibiotic. Patch tests with neomycin-containing ointments and/or 10% solution of this drug were positive in only about one-fourth of his cases. He concluded that, to establish the diagnosis, one had to rely on the results of the intradermal tests, which were positive in all of his cases.

Infection with antibiotic resistant staphylococci is becoming a major, national public health problem. Neomycin is the best topical therapeutic agent for treatment of staphylococcal skin infections because very few strains of staphylococcus are resistant to the antibiotic. Therefore, it is important to establish criteria for the recognition of contact sensitivity to neomycin, and, further, it is necessary to estimate the incidence of such reactions.

During the past three years we have made the diagnosis of contact dermatitis due to neomycin in 28 patients. This, for the most part, represents a selected group of patients, and the size of the series would seem to indicate a much higher incidence than is actually the case. Several of our patients had been seen prior to the start of our study, had used neomycin, and were recalled just for testing. During the past year, despite a high index of suspicion, we have seen only three new cases of neomycin sensitivity.

Report of Cases

In the Table we have summarized the pertinent facts on all of our patients. The following case reports are illustrative.

CASE 1.—A 37-year-old white man was first seen at this hospital on Aug. 1, 1955. A history was obtained of recurrent vesiculation on the sole of the right foot three or four times during the past seven years. The most recent episode began approximately one month before his first visit to the clinic. Treatment for this last exacerbation included x-ray therapy, a variety of ointments, and systemic antibiotic therapy. This resulted in temporary improvement, but two weeks later there was a relapse, and two days before we first saw him he had a severe exacerbation. At that time he had a 3 cm. patch of dermatitis on the sole of the right foot near the base of the toes, characterized by denudation, indolent inflammation, maceration, and multiloculated deep-set peripheral vesicles. The diagnosis was dyshidrotic eczema.

Submitted for publication Feb. 23, 1959.

From the Department of Dermatology, Henry Ford Hospital (Clarence S. Livingood, M.D., Chairman).

Because of failure to respond to local therapy on an outpatient basis, he was admitted to the hospital. With bedrest, systemic corticosteroids, compresses, and topical hydrocortisone he cleared in 12 days. On Aug. 13 he was discharged from the hospital and was instructed to use a neomycin-hydrocortisone ointment locally, three times per day.

He was then followed as an outpatient. However, vesiculation recurred, and on Aug. 27 he had to be readmitted because of swelling of the foot, pustulation, and adenopathy. There was an associated vesicular "id" on the fingers. Bacterial culture from the involved site at that time showed Pseudomonas aeruginosa as the predominant organism with many β-hemolytic streptococci. During the two weeks as an outpatient he had continued to use the neomycin-hydrocortisone preparation.

During this second admission he was treated with systemic corticosteroids and tetracycline. A neomycin-containing ointment was used topically from Aug. 27 to Aug. 30. There was no significant change in the character of the eruption during that time. On Aug. 30, the neomycin ointment was discontinued. On Sept. 1 it was noted that the vesicular eruption on the fingers was subsiding. Thereafter, there was a gradual but definite improvement. On Sept. 6, corticosteroids were discontinued. On Sept. 7, the lesion was completely healed.

On Sept. 10, tetracycline was discontinued, and he was started on neomycin-hydrocortisone ointment locally. Starting on Sept. 12, a gradual exacerbation was noted, with recurrence of vesiculation. This persisted through Sept. 15, at which time the neomycin-hydrocortisone was discontinued.

Corticosteroid therapy was reinstituted, and he improved gradually over the next two weeks. On Sept. 29, he was given prednisolone-tyrothricin-neomycin lotion to use locally. He was discharged on Sept. 30, still having some residual dermatitis.

However, on Oct. 3 he had to be readmitted because of a marked exacerbation. After this episode the possible relationship to neomycin was first suspected. Therefore, he was patch-tested to 0.5% neomycin ointment; he had a strongly positive reaction which was not maximal until about the seventh day. The patch-test site remained positive for seven weeks, and one year later, there was residual hyperpigmentation at the patch-test site.

After elimination of neomycin from his topical medications, he cleared gradually and has remained so since then.

The notable feature of this case was that the exacerbations of his eruption simulated relapse or recurrence of the original dermatitis, rather than a classical contact dermatitis. In fact, the clinical diagnosis which suggested itself to many observers was that of dermatitis repens.

Case 19.—A 49-year-old white woman was first seen on Aug. 2, 1955. A history of onset of otitis externa about two years prior to her first visit was obtained. Various types of local treatment had been used by a dermatologist, with partial improvement, but at no time had she had complete disappearance of this eruption. There was extension of the process and in the four weeks prior to her first visit she developed a dermatitis involving the antecubital fossae.

A combination of neomycin and fludrocortisone was prescribed. Two weeks later she had not improved significantly, and she was changed to 1% hydrocortisone ointment on the arms with continuation of the combined fludrocortisone-neomycin preparation to the ears. The dermatitis improved.

She did not return to the hospital until Feb. 24, 1956, at which time she was seen in the Ear, Nose and Throat Department, and it was noted that she had a severe otitis externa with involvement of the external ear and postauricular area. Neomycin-hydrocortisone drops of ointment were prescribed. Three weeks later it was noted that she had some improvement, and her treatment was continued. On March 3, 1956, the patient returned to the Ear, Nose and Throat Department, stating that she had had a flare-up of her dermatitis after she renewed her prescription. The neomycin-hydrocortisone ointment was discontinued, but the neomycin-hydrocortisone drops were continued.

She did not improve significantly and was, therefore, referred to the Dermatology Department. She had a relatively severe, more or less generalized eruption, together with the dermatitis of the auricles, the postauricular area, and the external auditory canals. She was given plain fludrocortisone lotion to the ears, and all previous treatment was discontinued. She was also given an antipruritic lotion, sedation, and an antihistaminic agent. Two days later she was much better, and 1% hydrocortisone ointment was added for selected sites. On April 6, 1956, she had had further improvement, and on April 13, 1956, she had continued to improve. On April 20, 1956, she returned with a recurrence of the dermatitis on her trunk and a rather general exacerbation. On questioning it was determined that she was using an ointment which was prescribed by a previous physician because she thought that the lotion was too drying—this ointment was probably neomycin-hydrocortisone. Again, all previous treatment was discontinued, and on April 25, 1956, she had marked improvement. She was seen at intervals until May 12, 1956, at which time it was noted that she had almost complete clearing in all areas of involvement, but she still had some drainage from the right ear canal. She was given 1% neomycin-

hydrocortisone ear drops, and when she returned on May 19, 1956, as well as May 26, 1956, and June 2, 1956, and June 23, 1956, she was relatively clear but on July 7, 1956, she again returned with a flare-up of her dermatitis. All treatment was discontinued except 1% hydrocortisone ointment, and she was started on grenz ray treatment. She was seen at intervals until Sept. 15, 1956, at which time she was completely clear.

She returned on April 3, 1957, because of a localized neurodermatitis on the dorsal surface of the feet. She stated that her otitis externa had been clear since she was last seen by us Sept. 15, 1956, and that she had used no medication, either ointment or ear drops. She volunteered the information that she had done better since "I stopped seeing doctors about my ears."

Because of her history of apparent exacerbations at times in the past, possibly associated with medication, particularly medicaments containing neomycin, we carried out appropriate patch and intradermal tests. She had markedly positive reactions to 1:100 aqueous solution neomycin intradermal tests, 1:1,000 aqueous solution neomycin intradermal tests, 1:100 aqueous solution neomycin patch test and 1:1,000 aqueous solution neomycin patch test, with the reactions more pronounced in all cases to the 1:100 solution. The intradermal tests to streptomycin and dihydrostreptomycin were read as negative, although there was a slight reaction to the 1:100 streptomycin.

The most distressing factor to the patient, and, we might add to her physicians, was that the patch and intradermal test sites were still strongly positive seven months later, after which time she was lost to follow-up.

This patient also manifested her sensitivity by an apparent gradual exacerbation of her otitis externa, rather than by an explosive acute episode.

CASE 18.—A 58-year-old white woman was first seen on Aug. 24, 1958, because of an eruption involving the external ears, sides of the neck, and periorbital regions.

The following history was obtained: Prior to this year she had a few transient episodes of otitis externa, not severe, and not requiring treatment.

In February, 1958, she developed bilateral otitis externa and was treated by her family physician and a consulting otorhinolaryngologist with neomycin-hydrocortisone drops and ointment with a resulting dramatic improvement. She continued to use the same topical therapy in a regular fashion. After about one month the eruption flared again and persisted more or less unchanged, except for periodic partial remissions and exacerbations up to the time we first saw her.

During the two months immediately preceding her first visit, there had been extension down to involve the sides of the neck and the periorbital regions. When this developed, her attending physician stopped all of her medications, both internal and external, with the exception of the neomycin-hydrocortisone ointment which was continued up to the time of her first visit to our clinic. She was also given systemic corticosteroids with no improvement.

Her previous history was essentially negative, except for "eczema" in infancy.

From the history, neomycin sensitivity was suspected and confirmed by a strongly positive patch test to a 1:100 solution of neomycin sulfate. Intradermal tests with 1:100 and 1:1,000 dilutions of neomycin sulfate were negative.

With simple topical therapy, consisting of 1% hydrocortisone cream, she cleared completely in four weeks.

This case also illustrates the insidious nature of the sensitivity. There was no acute flare, rather a gradual and persistent worsening of her primary problem.

CASE 6.—A 65-year-old white man was first seen on Sept. 15, 1954, because of pruritus ani of seven years' duration. Examination showed an eczematous dermatitis in the perianal area. He was treated with 1% neomycin-hydrocortisone lotion and used this medication until Oct. 7, 1954, with resulting complete relief of symptoms.

He was next seen on Nov. 20, 1956, at which time he stated that two weeks previously he had had a recurrence of pruritus ani. He first used calamine lotion with no relief of symptoms. He next used the 1% neomycin-hydrocortisone lotion which he had left over from his previous visits in 1954. Almost immediately, he had an acute flare-up with increased pruritus and extension of the eruption to the scrotum and inner thighs.

On examination there was an acute dermatitis involving the intergluteal spaces, the inner thighs, and posterior aspect of the scrotum.

Patch and intradermal tests to neomycin sulfate were positive.

He cleared rapidly with simple topical therapy.

This patient, who was the exception rather than the rule, showed a classical picture of acute contact dermatitis.

CASE 17.—A 54-year-old white man was first seen on Feb. 18, 1958, because of a severe conjunctivitis, associated with photophobia and almost constant lacrimation. There was an accompanying erythema and edema of the eyelids.

Symptoms began in November, 1957. An ointment of unknown type was prescribed by his family doctor with some relief. However, the conjunctivitis persisted, and he was next given a chloramphenicol (Chloromycetin) hydrocortisone ointment which he used for several weeks without significant relief.

He was then seen by an ophthalmologist, who prescribed a neomycin ophthalmic ointment on Feb. 1, 1958. He continued to use this until Feb. 13. He noted a flare-up of his conjunctivitis starting Feb. 6 and becoming progressively worse until Feb. 13, at which time he discontinued the ointment.

His previous history is significant in that during the period Nov. 6, 1954, to Jan. 8, 1955, he was treated topically with various neomycin-steroid combinations for a chronic eczematous dermatitis involving the medial aspect of the right ankle.

Patch tests to neomycin sulfate on Feb. 18, 1958, were strongly positive.

Because of the severity of his symptoms, systemic corticosteroid therapy was instituted on Feb. 18 and continued, with gradually decreasing dosage, for six weeks. Hydrocortisone lotion was used topically. He cleared completely over a period of two months.

CASE 15.—A 56-year-old white woman was first seen on Sept. 17, 1956, because of a pruritic erythematous eruption involving the left periorbital area and the left external ear.

The onset of the otitis externa occurred eight to nine months previously after a series of penicillin injections. She developed a generalized urticaria and then a persistent dermatitis of the ears.

She was treated with a variety of topical agents, including three or four different ointments with good results in the beginning. However, she continued to have a low-grade eruption involving primarily the left ear.

Four weeks previously she consulted an ophthalmologist for an unrelated problem. He gave her a tube of ophthalmic ointment, which was probably neomycin-hydrocortisone ointment, and instructed her to use it on her ears. After this, the dermatitis of the ears increased in severity and dermatitis of the left eyelid and the antecubital spaces appeared. She had continued to use the ophthalmic ointment.

Patch tests to the opthalmic ointment and to a neomycin-containing ointment were positive. Her eruption cleared over a period of several weeks.

She was next seen, two years later, on Nov. 25, 1958. At that time her presenting symptoms were an acute conjunctivitis, with associated redness and scaling of the upper and lower lids.

Two weeks previously she developed persistent pain in the left eye. An ophthalmologist made the diagnosis of corneal ulceration and prescribed a neomycin-hydrocortisone ophthalmic ointment. Within 24 hours she developed redness and scaling in the periorbital region, which persisted until we saw her, and was associated with conjunctival injection and edema.

Patch test to a 1% neomycin sulfate solution was positive. Intradermal tests to a 1:1,000 and 1:100 dilution of neomycin sulfate were negative.

After withdrawal of the neomycin and with simple local therapy this episode subsided over a period of four weeks.

This patient demonstrates the persistence of the sensitivity for a period of two years.

Patch Tests

The material used for patch-testing, in the earlier phases of our study, was the suspected ointment or lotion with appropriate controls. More recently, we have used a 0.1% and a 1% isotonic saline solution of neomycin sulfate.

Positive patch tests were obtained in 24 patients, questionably positive in two patients, and negative in two patients.

The patch-test material was removed after 48 hours, at which time the tests were usually read as negative. Usually, positive tests became evident in from three to five days.

We also noted a definite tendency for the positive patch-test sites to become chronically eczematized and to persist for several weeks. Five to seven weeks was the usual duration. Case 19 illustrates the extreme in this observation in that the test sites, both patch and intradermal, were eczematized seven months after the initial application.

Intradermal Tests

Intradermal testing, using 0.1 cc. of neomycin sulfate in isotonic saline solution in 1:1,000 and 1:100 dilutions, were performed in 19 patients in this group.

In nine patients both the patch and intradermal tests were positive. In two patients the intradermal tests were positive, the patch tests negative. In five patients the intradermal tests were negative, the patch tests positive. In two patients the intradermal tests were positive, the patch tests questionably positive.

No attempt will be made to draw any conclusions from these findings. It is pertinent to note that, in contrast to Epstein's findings,[3,4] positive patch tests were noted in 24 out of 28 patients.

Comment

With few exceptions, e. g., Cases 6, 15, and 17, the development of neomycin

sensitivity was an insidious process. In these three patients, there was a definite correlation between use of a neomycin-containing preparation and the onset of an acute exacerbation.

On the other hand, the majority of patients in our series were suspected of neomycin sensitivity because of a gradual progression of their eruption and failure to respond to what would be considered adequate therapy. In this group there was no clear-cut relationship between use of a neomycin-containing preparation and progression of dermatitis. The use of neomycin did not cause an acute exacerbation.

In some patients, notably Cases 1 and 19, the use of a neomycin-containing topical preparation caused an exacerbation, which was interpreted at the time as being a flare-up of the underlying dermatitis.

While we do not have enough patients from which to draw rigid conclusions an analysis of the primary sites of involvement (Table) would seem to support our clinical impression that sensitization may be more apt to occur if the involved site is an intertriginous area, or subject to maceration. However, the predominance of otitis externa in our series may only be a reflection of the widespread use of neomycin-containing topical steroids in this situation and the chronicity of the problem.

In conclusion, we feel that neomycin contact sensitivity is not common. Despite an

Neomycin Sensitivity in Twenty-Eight Patients

Case No.	Age	Race	Sex	Primary Site of Involvement	Diagnosis	Preparation Used	Patch Test	Intradermal Test
1	37	W	M	Foot	Ecz. dermatitis	Various neomycin & neomycin-hydrocortisone preparations ointment & lotion	+	Not done
2	35	W	F	Ears	Otitis externa	Neomycin-hydrocortisone ointment	+	Not done
3	56	W	F	Ears	Otitis externa	Combination neomycin, polymyxin B & bacitracin ointment, neomycin-hydrocortisone ointments	+	+
4	56	W	M	Foot	Ecz. dermatitis	Neomycin-polymyxin B, bacitracin ointment	+	+
5	27	W	F	Hands	Ecz. dermatitis	Neomycin-hydrocortisone ointment & lotion	+	−
6	65	W	M	Perianal	Pruritus ani	Neomycin-hydrocortisone lotion	+	+
7	56	W	F	Hands	Ecz. dermatitis	Neomycin-hydrocortisone ointment	+	−
8	28	W	M	Ears	Otitis externa	Neomycin-hydrocortisone ointment	+	−
9	47	W	F	Axillae	Ecz. dermatitis	Neomycin-hydrocortisone lotion	+	Not done
10	36	W	F	Ears	Otitis externa	Neomycin-hydrocortisone ointment	+	Not done
11	60	W	F	Hands	Ecz. dermatitis	Neomycin ointment & lotion	+	Not done
12	50	W	F	Foot	Ecz. dermatitis	Neomycin ointment; neomycin-fluorinated hydrocortisone lotion	+	Not done
13	35	W	F	Hand	Ecz. dermatitis	Neomycin-hydrocortisone lotion	+	Not done
14	36	W	M	Legs	Ecz. dermatitis	Neomycin-hydrocortisone lotion	+	Not done
15	56	W	F	Ears	Otitis externa	Neomycin ointment	+	−
16	54	W	M	Ears Perianal	Otitis externa Pruritus ani	Neomycin ointment Neomycin-hydrocortisone ointment	+	+
17	54	W	M	Eyes	Conjunctivitis	Neomycin ointment	+	Not done
18	58	W	F	Ears	Otitis externa	Neomycin-hydrocortisone ointment	+	−
19	49	W	F	Ears	Otitis externa	Neomycin fluorinated hydrocortisone	+	+
20	16	W	F	Face	Ecz. dermatitis	Neomycin ointment Neomycin-hydrocortisone ointment	− +	+ +
21	14	W	M	Hands	Ecz. dermatitis	Neomycin-hydrocortisone ointment	−	+
22	49	W	M	Hands	Ecz. dermatitis	Neomycin-hydrocortisone ointment	+	+
23	45	W	M	Perianal	Pruritus ani	Neomycin-hydrocortisone ointment	Questionable	+
24	24	W	F	Axilla	Contact dermatitis	Neomycin-hydrocortisone ointment	+	+
25	35	W	F	Ankle	Ecz. dermatitis	Neomycin-hydrocortisone ointment	+	+
26	62	W	F	Eyelids	Ecz. dermatitis	Neomycin-polymyxin B-hydrocortisone ointment	Questionable	+
27	5	W	F	Toes	Ecz. dermatitis Atopic dermatitis	Neomycin ointment	+	+
28	65	W	F	Ears	Otitis externa	Neomycin-hydrocortisone ointment	+	+

increased index of suspicion, we have seen only three cases during the past year. However, the possibility should be borne in mind especially in a patient with an eczematous dermatitis, using a neomycin-containing preparation, who is not responding satisfactorily.

In all of our patients, symptoms and signs regressed promptly after elimination of neomycin.

Summary

Neomycin sensitivity is not common. However, the onset may be insidious and its recognition depends upon a heightened index of suspicion, rather than on the appearance of the classical signs of acute contact dermatitis.

A total of 28 patients with neomycin sensitivity have been observed by us. Illustrative cases are described.

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Threshold Stimulation of the Skin and Housewives' Eczema of the Hands

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In a previous study [1] on cutaneous sensibility threshold measurement with square-wave current, two significant findings were reported: (1) The range of sensibility thresholds was higher in men than in women, and (2) in women with housewives' eczema of the hands the sensibility threshold range was lower than in other women. It was felt that these differences in threshold sensibility were basically related to epidermal thickness rather than to neurological differences. Inasmuch as the outer epidermis acts as a protection against all outside irritants, it was felt that epidermal thickness would also influence the reaction to primary irritants. It was, therefore, theorized that in thin-skinned persons, the sensibility threshold would be relatively low and resistance to primary irritant would also be relatively low, resulting in a greater primary irritant reaction. The opposite course of events would be expected in relatively thicker-skinned persons.

The opinion that housewives' eczema of the hands is a primary irritant dermatitis has often been expressed.[2-7] Having previously found that these patients show a relatively low sensibility threshold range, it was further theorized that these persons are relatively thin-skinned and would probably have greater reactions to primary irritation. The present study was undertaken in order to demonstrate this relationship between sensibility threshold, primary irritant reaction, and housewives' eczema.

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Experimental Set-Up

Forty-three patients attending the Grace-New Haven Community Hospital Skin Clinic were selected for the experiment. Of these, 30 were women, 12 of whom were diagnosed as having housewives' eczema of the hands. Thirteen men and eighteen women with miscellaneous dermatoses acted as controls. The following routine was adhered to as closely as clinic conditions would permit:

1. Each subject was first tested for sensibility threshold with threshold voltage (TV) measurements taken at the antecubital area with the apparatus and technique described below.

2. Patch tests of cantharidin solution in acetone were then applied to the contralateral antecubital area. Patch tests were made by wetting the small gauze pad of a plastic "spot" bandage which was then applied to the skin and occluded with adhesive tape. The threshold dilution of cantharidin was found to be 0.01%.

3. The patch tests were read in 24 hours. A blister reaction was read as positive; a nonblister reaction, with or without erythema, was read as negative. At this time also the TV measurement was repeated.

4. A third TV measurement was repeated again in 48 hours. The TV readings were averaged and recorded as the sensibility threshold.

Apparatus and Technique of Threshold Voltage Measurement

The source of the electrical square-wave impulse is a Grass, Model S-4, stimulator which has been calibrated to within ±5% accuracy for each parameter. Frequency is fixed at 50 cps and impulse duration for 0.1 msec.

The patient is placed on an examination table relaxed and supine. The active electrode, which consists of a curved ECG arm electrode padded with saline-moistened gauze, is applied to the normal skin of the antecubital area and kept in place with the wide, perforated rubber band customarily used with ECG electrodes. Very little tension is applied to the rubber band so as not to crease or depress the skin. The indifferent electrode

consists of a large piece of lead-tin material similarly padded and applied to the leg.

Threshold voltage readings are obtained by increasing the voltage until a vibrating or prickly sensation is first perceived by the subject in the area covered by the active electrode. The voltage is then decreased until the sensation disappears and increased again, this time more slowly, to ascertain the minimal voltage required to produce the threshold sensation. This process can easily be repeated several times within a few minutes until the examiner is satisfied that the threshold voltage (TV) readings are valid and accurate.

Comment

Sensibility Thresholds.—Individual variations in sensibility thresholds were previously [1] found to average about ± 15% when tests were repeated in 30 minutes. In this study, where tests were repeated 24 to 48 hours apart, and in unpublished data, in subjects examined at weekly or monthly intervals over a period of several months to a year, the variations in readings were of the same order. It is thus clear that the threshold voltage is variable within a limited range. A single TV reading is not apt to be as accurate as the average of several readings taken 30 minutes or more apart.

In unpublished data from more than 1,000 readings in about as many subjects, no significant differences in the sensibility threshold range were found by reason of age, race, skin complexion, or reason of the year, nor were the thresholds in 30 of these cases influenced by various phases of hyperthyroidism.

Cantharidin.—Cantharidin solution of 0.01% was found to be of threshold strength, inasmuch as stronger solutions invariably produced blisters and weaker solutions produced no blisters on subjects tested. It was necessary to guard against concentration of the solution by evaporation of the acetone. Fresh solutions were made periodically and tested against each other. Refrigeration of the cantharidin solution helped reduce evaporation. The primary irritant reaction of cantharidin seems to follow an all-or-none pattern, inasmuch as the reaction was either bullous or negative. Erythema was infrequently found with the threshold dilution even when a bulla developed. For this reason the reactions were not graded but listed as positive or negative for blister formation.

Housewives' Eczema of the Hands.—The diagnosis of housewives' eczema of the hands in this study was made by exclusion of other diseases (atopic dermatitis, contact dermatitis, psoriasis, nummular eczema, neurodermatitis, dyshydrosis, and seborrheic dermatitis). There was in each case a history of excessive use of soaps, detergents, or other mild primary irritants in household work, in care of infants and young children, or in laboratory work among hospital personnel. The dermatitis in all cases was chronic and recurrent, having been present for at least six months.

Results

Correlation of blister reactions to TV in the entire group of 43 subjects shows the following relationship (Table 1):

1. Subjects with average TV of 10 volts or less tend to develop a blister reaction to the threshold cantharidin solution (87% positive).
2. With average TV between 10 and 13 volts, positive and negative blister reactions tend to be more evenly distributed (36% positive).
3. Subjects with average TV of 13 volts or more tend not to develop blister reaction to threshold cantharidin solution (6% positive).

The results were interpreted as indicating that there are three critical areas of TV values with respect to the threshold blister reaction, viz., low TV (10 volts or less) associated with high degree blister response, medium TV (between 10 and 13 volts) associated with equivocal blister response, and high TV (13 volts or higher) associated with little blister response. Because of

TABLE 1.—*Entire Group of Forty-Three Cases*

TV	No. Cases	Pos. Blister		Neg. Blister	
		No.	%	No.	%
Low	15	13	87	2	13
Med	11	4	36	7	64
High	17	1	6	16	94

TABLE 2.—*Males, Thirteen Cases, Compared to Females, Thirty Cases*

	No. Cases		Pos. Blister		Neg. Blister	
TV	M	F	M	F	M	F
Low	1	14	1	12	0	2
Med.	2	9	0	4	2	5
High	10	7	1	0	9	7

this relationship, it was considered more feasible, in the statistical analysis, to grade TV as high, medium, or low rather than specific averaged TV readings. In the group as a whole, it was thus generalized that there is a negative association between TV values and blister reaction to threshold cantharidin solution, those with low TV showing a higher proportion of positive blister reactions than those with high TV ($P<0.001$).

When the statistics are broken down according to sex, males (Table 2) are shown to have a higher TV on the average than females ($P<0.001$). However, for a given TV value, no difference was found in susceptibility to threshold cantharidin solution between males and females.

A breakdown of the women into subjects with housewives' eczema of the hands and and other women (Table 3) shows that high TV is uncommon in women, and when it is found is less likely to be associated with housewives' eczema of the hands than with other dermatoses ($P<0.01$). Furthermore, the group with housewives' eczema of the hands is less resistant to threshold cantharidin solution than the control group ($P<0.05$).

TABLE 3.—*Females with Housewives' Eczema, Twelve Cases, Compared to Other Females, Eighteen Cases* *

	No. Cases		Pos. Blister		Neg. Blister	
TV	HE	OF	HE	OF	HE	OF
Low	7	7	7	5	0	2
Med.	5	4	3	1	2	3
High	0	7	0	0	0	7

* HE indicates housewives' eczema; OF, other females.

Comment

Aside from the fact that the outer epidermis acts as a general protection against all outside irritants, it is difficult to establish other factors in common to account for the correlation in responses here obtained to electrical and chemical stimulation of the skin, except perhaps the anatomical epidermal thickness which lies between the stimulus and the target nerve or epidermal cells respectively.

Electrical threshold stimulation of the skin is essentially threshold stimulation of the prick receptors which lie just below the epidermis, inasmuch as these nerve endings as described by Bishop [8] have the lowest threshold of the cutaneous sensory receptors to electrical stimulation. Montagna,[9] however, states that free cutaneous nerve endings, said to be pain receptors (? prick receptors), lie among the epidermal cells. The cutaneous response to repetitive electrical stimulation at any fixed impulse duration depends principally on the strength of the stimulus (voltage) and the physiological state of the nervous system. As the electrical current passes through the epidermis, the strength of the stimulus is altered by electrical skin resistance, which in turn is influenced by such variables [10] as temperature, humidity, sweating, and epidermal thickness separating the active electrode from the nerve receptors.

The cutaneous response to chemical stimulation depends principally on the strength of the solution and its ability to reach the epidermal cells and/or dermal-epidermal junction. Rostenberg,[11] in a review of the literature on the mechanism of blister formation, finds that evidence is not conclusive as to whether the primary lesion in the development of a vesicle is a liquefaction of the epidermal cells or an alteration in the permeability of a capillary at the epidermal-dermal junction. He states that thickness of the horny layer, as well as local vascularity and pH, also play a role in the response to threshold concentration of a primary irritant.

It appears from this that both types of stimuli must pass through horny layers and some amount of epidermal cell layers in order to produce their respective responses. Other factors also influence the strength of both stimuli. However, the basic influence common to both stimuli appears to be the anatomical thickness of the tissue traversed.

Although the gross responses, based as they may be in common on epidermal thickness, seem to mirror each other, finer differences in responses may be anticipated because of their intrinsic differences and the other divergent influences on both types of stimuli. Some of these response variations were demonstrated in a single self-applied experiment with cellophane-tape stripping of the active electrode area. Before stripping, a high TV value was found associated with a negative blister reaction. After three strippings of the electrode area, the TV was unchanged, but the blister reaction became positive. After 10 strippings of the electrode area, the TV value dropped to the low range, blister reaction was obtained to threshold cantharidin solution in the stripped area, and the contralateral control area maintained a high TV value. Further investigation in this direction may help clarify the role of keratin thickness in blister reaction, the relative depth of sensory receptors, and the rate of regrowth of epidermis.

To the extent that epidermal thickness influences the sensibility threshold, the sensibility threshold conversely may become a measurement, albeit crude and indirect, of the epidermal thickness, and consequently of skin protectivity. In this light one might explain the mechanism of housewives' eczema as developing in women with predominantly low TV values because of relatively thin epidermis. The thin epidermis, coupled with the challenge of frequently used mild irritants (soap, etc.) may give rise to the syndrome. However, further investigation is needed to determine whether the antecubital area is representative of other body sites, inasmuch as the sensibility threshold has been found to vary in different body sites.[12]

The finding that a high TV value is less likely to be associated with housewives' eczema of the hands than with other dermatoses in women suggests that this finding may be of value in the differential diagnosis of hand eczemas. If low TV values can be found, on further investigation, to be associated with greater reactivity to the challenge of other primary irritants or primary irritation in general, such measurements may be of prophetic and prophylactic value, wherever mild primary irritants are in great use, as in certain industries and occupations. Rostenberg,[11] in this vein, also suggested that on the basis of "the differences to the way persons respond to various stimuli . . . predictions might be made as to the suitable milieu for a given person."

Summary and Conclusions

The premise was made that the sensibility threshold response was related to the threshold primary irritant response through the influence that epidermal thickness has in common on both types of stimuli. It was thus predicted that where sensibility threshold was low, the resistance to primary irritant would also be low as manifested by a blister reaction, and vice versa. In this connection, patients with housewives' eczema of the hands, having previously been found to have a low sensibility threshold range, would be expected to show greater reactivity to a primary irritant than a control group.

Forty-three patients, of whom thirteen were males; twelve, females with housewives' eczema of the hands, and eighteen, females with miscellaneous dermatoses, were studied with comparative threshold electrical (square-wave) and chemical (cantharidin) stimulation. The group was studied (1) as a whole, (2) on the basis of sex, and (3) on comparison of subjects with housewives' eczema of the hands with females with other dermatoses.

The results indicated that high threshold voltage (TV) was associated with high resistance to threshold primary irritant and vice-versa. Males were found to have higher TV values on the average than females, but for a given TV value there was no difference in susceptibility to primary irritant between males and females. Patients with housewives' eczema of the hands were found less likely to have a high TV and also showed less resistance to the primary irritant than other women.

The results were interpreted as indicating that TV might be considered as a crude, indirect measurement of epidermal thickness so that low TV values are indicative of a relatively thin epidermis. On this basis, the mechanism of housewives' eczema of the hands could be explained as a combination of thin epidermis and chronic or frequent exposure to mild primary irritants.

Further implications of this study were discussed with respect to the diagnostic, prophetic, and prophylactic use of sensibility threshold measurements.

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Intermediary Metabolism of Phenylalanine and Tyrosine in Diffuse Collagen Diseases

II. Influences of the Low Phenylalanine and Tyrosine Diet upon Patients with Collagen Disease

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Previously, we [1-3] reported the constant and specific presence of 2,5-dihydroxyphenylpyruvic acid, an imaginary intermediary metabolite of phenylalanine and tyrosine, in urine of diffuse collagen disease patients, and that L-tyrosine dosage unfailingly aggravated both clinical signs and laboratory data of collagen disease. Founded on these facts, low phenylalanine and tyrosine dietary treatment has been performed on 26 diffuse collagen disease patients with good results in both clinical signs and laboratory data.

Commonly, high-protein diet has been recommended for the treatments of collagen disease and also a few specific dietary treatments [4-14] have been known.

Many investigators [15-18] obtained good results in mental deficiency of phenylketonurics on well-defined synthetic diets deficient in phenylalanine.

Armstrong and Tyler and Woolf et al. suggested that the phenylalanine-restricted diet should be initiated at a very early age in order to prevent irreversible damage to the central nervous system.

The influence of phenylalanine and tyrosine upon growth and metabolism in vivo of man and rat have been considerably investigated from biochemical and pathological points of view.

Berg and Rose and Geiger [20] had stated that the formation of protein molecules could be completed only when all amino acids which participate in its production in cooperation with tissue formation were present, and when certain essential amino acids were absolutely or relatively lacking, the incomplete amino acid products which would not be utilized for protein formation would not be stored in the body but irreversibly further metabolized.

Madden, Finch, Swalback, and Whipple [21] stated that amino acids necessary for plasma protein formation in dogs were not necessarily identical with those for total body growth and maintenance. Tyrosine is also essential for the formation of plasma protein as cystine, leucine, and glutamic acids.

Rose, Haines, and Johnson [22] stated that only 10 amino acids were as capable of maintaining nitrogen equilibrium in man as in rats and dogs.

In regard to the minimal requirement of phenylalanine of a man, there is a series of reports by Rose, Leach, Coon, and Lambert.[23] They administered diets consisting of pure amino acid mixtures as nitrogen sources maintaining on positive nitrogen balance and concluded that the daily minimal phenylalanine requirement for normal adult men was 1.1 gm. and the safe intake 2.2 gm. from the measurement. Approximately 0.5 gm. per day of D-phenylalanine can be utilized, but negative nitrogen lasted even if daily intake was beyond 1.19 gm. At a level equal to or slightly in excess of a person's minimal L-phenylalanine requirement, DL-phenylalanine appeared to be almost as effective as the L-isomer; in a

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group of 28 normal men, 2.40 gm. of daily intake or even less of DL-phenylalanine was sufficient to keep the positive nitrogen balance.

Many investigators [24-33] found that weanling rats fed on diets deficient of essential amino acids (phenylalanine, threonine, histidine, isoleucine, tryptophan, and so on), revealed similar or the same changes of various organs: regressive changes of acidophils of the anterior lobe of the pituitaries; cellular atrophy of the zona glomerulosa of the adrenal cortex; atrophy of the testes, epididymides, ventral prostates, and seminal vesicles; retarded bone growth; atrophy of the thymus glands, and depression of growth. The degeneration of these organs, however, was completely reversible with subsequent administration of adequate diets. Therefore, it is suggested that the primary effect of the deficiency is on the pituitaries.

Maun et al.[24] and Schwartz et al.[25] have described a simultaneous decrease of hemoglobin contents, serum protein, and loss of weight, along with the above-mentioned regressive tissue changes caused by low-phenylalanine diet. In this connection, they suggested that the phenylalanine was a necessary ingredient to produce trophic hormones in the anterior lobe of the pituitary gland. However, Schwartz et al. reported that the above-mentioned regressive tissue changes were not found in rats fed on only tyrosine-deficiency diet and that normal health was maintained. Grau and Steele [34] found in an experiment on young mice fed with a phenylalanine-deficient diet, labeling the phenylalanine with C^{14}, that conversion of the phenylalanine to tyrosine and to CO_2 in the liver becomes much decreased, and on an adequate diet of amino acids (except phenylalanine), the available phenylalanine for conversion to tyrosine and to CO_2 becomes very limited because of more utilization for the formation of protein. On the other hand, even with excess of the amount of phenylalanine in the diet for normal growth, there is no proportionate increase of the synthetic ratio of liver protein, but the phenylalanine is stored as tyrosine to be converted to CO_2.

Much of the literature,[35-39] however, reveals that inhibition and delay of normal growth can be caused by a diet with an excess of essential amino acids, and there are some reports of marked growth depression of young mice and chicks by an excess of phenylalanine or tyrosine in the diet. Benton, Harper, Spivey, and Elvehjem [38] reported that the growth of mice was much depressed when 3% of DL-phenylalanine was added to the diet containing 9% casein as protein resource, but, on the contrary, adding the phenylalanine could not cause inhibition of growth if the casein in the diet was 18%. These facts suggested the presence of some antagonistic amino acids against phenylalanine. The growth rate of rats fed a 9% casein diet supplemented with tryptophan and methionine was markedly depressed by supplementation of either 3% of DL-phenylalanine or 3% of L-tyrosine. A supplement of threonine prevented this effect in both cases. Threonine alone did not prevent the growth depression caused by phenylalanine when tryptophan was not added to the diet. Therefore, phenylalanine was thought to be the antagonist of threonine.

Harper et al.[40] has found decreased activities of tyrosine oxidase in homogenated liver of male weanling rats fed on basic casein diet, but, by adding threonine to this diet, the activities of tyrosine oxidase were increased fourfold. Therefore, as a conclusion, they stated that lack of threonine in a diet disturbed the synthesis of enzymes that participate in the metabolism of phenylalanine and tyrosine.

Experimental Results

1. The patients treated on this low phenylalanine and tyrosine diet were all hospitalized patients, and the dietary treatment was initiated in one week after hospitalization. During the first week after

hospitalization, laboratory examinations were carried out on them on regular house diet. The duration of dietary treatment was about 20 to 75 days or more, and during this time specific treatment with cortisone, prednisolone, or corticotropin (ACTH) was avoided. The patients who could not endure this dietary treatment or left a large amount of food of the diet were omitted from our routine experiments.

2. As the protein source we selected Jellice,* a refined and edible form of gelatin [41] containing minimum amounts of phenylalanine and tyrosine. Commonly, it has been said that absorption of gelatin from the alimentary tract is not so good, the absorption rate being less than 70%, although this figure differs from author to author. But absorption of Jellice is superior to that of gelatin, and it is suggested that its absorption is almost complete. Jellice alone is monotonous, and patients have distaste for continuing the diet, and so 20 gm. of whale, cod, or herring [41] containing a small amount of phenylalanine and tyrosine were added to it as the protein source. For carbohydrates, fats, vegetables, and fruits, those which contain a negligible amount of phenylalanine and tyrosine were selected.

Supposing the absorption rate of Jellice is 90% and the protein content of whale, cod, or herring is 20%, the phenylalanine content is calculated to be 1.1 gm. and, tyrosine 0.2 gm. in the 80 gm. of mixture diet of Jellice and whale, cod, or herring. Those amounts of phenylalanine and tyrosine are almost equal to minimal requirements of phenylalanine of adult figured by Rose et al.[23]

A summary of low phenylalanine and tyrosine diet is shown in Table 1. The daily menu, prepared on the above-mentioned low phenylalanine and tyrosine base is shown in Table 2.

* Jellice is manufactured by Miyagi Chemical Industrial Co., Ltd., Sendai, Miyagi Pref., Japan.

TABLE 1.—*Low Phenylalanine and Tyrosine Diets for Collagen Disease Patients* *

	Daily Intake		Remarks	
	Food	Amount, Gm.	Phenylalanine, % in Protein	Tyrosine, % in Protein
	Jellice,	60	1.4-2.5	0.2-0.4
	Whale, or	20	2.6	2.4
	Cod	20	1.3-2.3	2.5
	Herring	20	2.8	2.5
Carbohydrate	Starch	300	(—)	(—)
Fat	Margarine	25	(—)	(—)
	Vegetable oil	20	(—)	(—)
Vegetable	Pumpkin, onion, radish, carrot, cabbage, colts' food	Proper quantity	Extremely low	
Fruit	Apple, orange, tomato, strawberry	Proper quantity	Extremely low	

* 1. In general, dietary protein contains 4%-6% phenylalanine and total diet contains 0.4% L-tyrosine and 0.04% L-tryptophan, respectively.

2. Sugar and sodium chloride; freely given; soy sauce and Worchestershire sauce, restricted. Total about 2,300 cal.

3. Daily medication: DL-tryptophan, 0.5 gm., and DL-valine, 1.0 gm. (because of extremely low components of tryptophan and valine in Jellice); DL-methionine, 3.0 gm.; Panvitan M (rich in vitamins and minerals), 3 tablets (Takeda Pharmaceutical Ind., Ltd., Japan).

4. The diet is adequate to permit normal health and exerts no specific side-effects on the patients.

5. Effects usually begin to appear 1-2 weeks after starting this dietary treatment.

TABLE 2.—*Sample of a Menu for Collagen Disease Patients*

Menu	Materials	Weight, Gm.	Cal.
	(A)		
	Starch	150	510
Starch cake	Sugar	20	80
	Sodium glutaminate	a little	
	Jellice	15	
Fruit jelly	Water	200	
	Pear canning	70	12.3
	Sugar	20	7.5
	Soup	180	4.1
	Whale	10	
Soup	Onion	30	
	Carrot	10	
	Jellice	3	
	Sodium glutaminate	2	
	Cucumber	70	6.3
	Onion	50	12.5
	Carrot	30	12.5
French salad	Salad oil	10	90
	Vinegar	10	
	Sugar	5	45
	Sodium glutaminate	2	
Total			881.4
	(B)		
	Starch	150	51.0
Starch cake	Bitter orange juice	50	14
	Sugar	20	80
	Sodium chloride	2	
	Jellice	15	
Fruit jelly	Water	200	
	Sugar	20	80
	Loquat canning	70	63.7
	Soup of whale	75 c.c.	
	Jellice	15	
Aspic	Cucumber	50	4.5
	Onion	20	8.2
	Sodium glutaminate	a little	
	Sodium chloride	2	
	Pumpkin	100	58
	Onion	50	12.5
	Carrot	50	20.5
Boiled vegetable	Sugar	10	40
	Salad oil	15	135
	Orange juice	50	24
Juice	Sugar	25	100
	Jellice	3	
	Water	180	
Total			1,141.4
	(C)		
	Starch cake	150	501
Starch cake	Sugar	20	90
	Sodium chloride	2	
	Jellice	15	
Fruit jelly	Water	200	
	Sugar	20	
	Pineapple	70	60.2
	Bitter orange juice	100	28
	Jellice	5	
Juice	Water	120	
	Sugar	20	90
	Essence of lemon	a little	
	Onion	150	12.3
Boiled vegetable	Whale	10	37.5
	Margarine	10	73.8
	Sodium chloride	2	
Fruit	Apple	150	64.5
Total			937.3
	Other Miscellaneous Menus		
	Soup of whale	100	
	Radish	100	16
Boiled radish	Sugar	10	40
	Oil	5	45
	Sodium chloride		
Total			101
	Bitter orange juice	50	14
Hot juice	Water	100	
	Sugar	25	100
	Jellice	5	
Total			114
	Radish	150	24
	Carrot	20	8.2
Boiled radish	Fat	5	45
	Sodium chloride		
	Sugar	10	40
Total			117.2
"Temmpura" (Japanese fry)	"Harusame"	10	32.9
	Onion	50	12.5
	Carrot	30	12.3
	"Kudzu"	20	66.8
	Fat	15	135
Total			139.5

Details of the patients treated with this diet are shown in Table 3.

Effects of this Dietary Treatment upon Clinical Symptoms

1. Dermatomyositis

CASE 1.—A 51-year-old man.

By this dietary treatment, the patient regained grasping power and began to walk without a crutch, without which the patient was unable to walk before, and climb stairs without stumbling. Dysphagia and dyslalia were corrected; weakness, stiffness, and atrophy of the muscles of the extremities and the shoulder girdle were gradually recovered. Abnormal pigmentation of the skin gradually faded, and he regained the almost normal color. The patient was discharged after 75 days on this diet and continues to be in a good condition of health without relapse on regular diet till date for a year and one-half.

TABLE 3.—*The Patients Treated on This Diet*

No.	Disease	Age	Sex
1	Dermatomyositis	51	M
2	Dermatomyositis	12	F
3	Generalized scleroderma	41	F
4	Generalized scleroderma	18	F
5	Acrosclerosis	28	M
6	Acrosclerosis	26	M
7	Chronic discoid lupus erythematosus	40	F
8	Chronic discoid lupus erythematosus	43	F
9	Chronic discoid lupus erythematosus (with acute exacerbation)	40	F
10	Rheumatoid arthritis	24	F
11	Rheumatoid arthritis	43	M
12	Rheumatoid arthritis	51	F
13	Rheumatoid arthritis	51	M
14	Rheumatoid arthritis	11	F
15	Rheumatoid arthritis	45	F
16	Rheumatoid arthritis	52	M
17	Rheumatoid arthritis	34	F
18	Rheumatoid arthritis	27	F
19	Rheumatoid arthritis	51	F
20	Rheumatoid arthritis	26	F
21	Rheumatoid arthritis	22	F
22	Rheumatoid arthritis	24	F
23	Rheumatoid arthritis	24	F
24	Rheumatoid arthritis	31	F
25	Rheumatoid arthritis	43	F
26	Rheumatoid arthritis	48	F

CASE 2.—A 12-year-old girl.

The muscles and skin of the extremities became soft. The atrophy of the extremities, especially of the lower extremities, was corrected, regaining the normal contour and strength to walk. Patient walked without stumbling and could sit straight up.

2. Generalized Scleroderma

CASE 1.—A 41-year-old woman.

This patient was admitted at a progressive stage. By the treatment, progress of the disease was halted, and edema of extremities receded. After 30 days of this dietary treatment the patient walked out of the hospital for a personal reason, after which there was rapid aggravation of the lesions.

CASE 2.—An 18-year-old girl.

This patient was admitted at a late stage, presenting sclerosis of extremities, including the hands, face, and breast, especially remarkable in both hands and forearms, besides atrophy and contracture of the hands and ankylosis of the joints of the phalanges, wrists, and ankles. The patient complained of mild dyspnea and difficulty in walking. After 30 days on this dietary treatment, there was softening of the skin of the extremities, face, and breast; disappearence of dyspnea; recovery of difficulty in walking; subsidence of ankylosis of the ankle joints; healing of ulcers of the fingers, and greater flexibility of the elbow joints observed, although ankylosis of the wrists and finger joints remained unchanged with this treatment of 30 days. Further dietary treatment is being performed on this patient.

3. Acrosclerosis

CASE 1.—A 28-year-old man.

This patient was admitted eight years after the onset and presented intense ankylosis of the joints of fingers and toes. By this treatment, the patient showed remarkable softening of the skin of the fingers and toes, as was seen previously with prednisolone, although ankylosis of the joints and atrophy of the fingers and toes remained unchanged.

CASE 2.—A 26-year-old man.

After the treatment, remarkable softening of the skin of the hands and both forearms occurred, stiffness of the face subsided, and, moreover, range of motion of finger joints and grasping power increased. However, changes of finger nails remained the same.

4. Chronic Discoid Lupus Erythematosus

CASES 1 and 2.—A 40-year-old woman and a 43-year-old woman.

Almost complete recovery to normal skin was observed in both of the two cases; in about 10 days after the initiation of the treatment the erythematous lesions began to recede and gradually dry, regaining almost normal skin texture.

5. Chronic Discoid Lupus Erythematosus with Acute Exacerbation

CASE 1.—This patient was hospitalized because of erythematous and scaly lesions of the fingers, the feet, and the surrounding area of the mouth, which had been irresponsive to various treatments, and repeated episodes of pyrexia. The temperature came down on the fifth day after the diet was started, and normal temperature continued thereafter. After 20 days of this treatment, the erythematous scaly lesions were alleviated. The ulcerative lesion of the left foot, which did not respond to various other treatments, was gradually cleared from the 20th day of this treatment, and good granulation occurred in 30 days on the diet and pain of the lesion almost disappeared.

6. Rheumatoid Arthritis

Generally, this treatment was most effective on moderately advanced cases.

(*a*) Subjectively there was alleviation of pain, spontaneous on movement as well as on weight bearing, of all the involved joints.

(*b*) Objectively, swelling and heat of joints were markedly decreased. In the joints of fingers, toes, and wrists, improvement occurred in every form of rheumatoid

arthritis. At an early stage of arthritis, hydrops of large joints as elbow and knee, receded or were cured. Hydrops at a progressive stage with deformities of the joints revealed no apparent improvement but remarkable subsidence of stiffness on arising. There was, in a case of granulation form, amelioration of pain but without much change of the objective findings. It is an interesting fact that a patient who had been on cortisone required only half of the usual dosage, and the effect was prolonged twice as long. It was observed, however, that discontinuation of the dietary treatment often reversed the clinical signs and symptoms.

Effects of This Dietary Treatment upon Laboratory Data

Body Weight.—There was not a significant change observed except when complicated by other disease.

Blood Picture.—No marked changes occurred in the count of red and white cells and in hemoglobin concentration.

Erythrocyte Sedimentation Rate.—This was not altered remarkably. In rheumatoid arthritis improvement of clinical symptoms was paralleled with that of the erythrocyte sedimentation rate.

Serum Protein (hand reflectometer, Hitachi Ltd., Co.).—In general, total serum

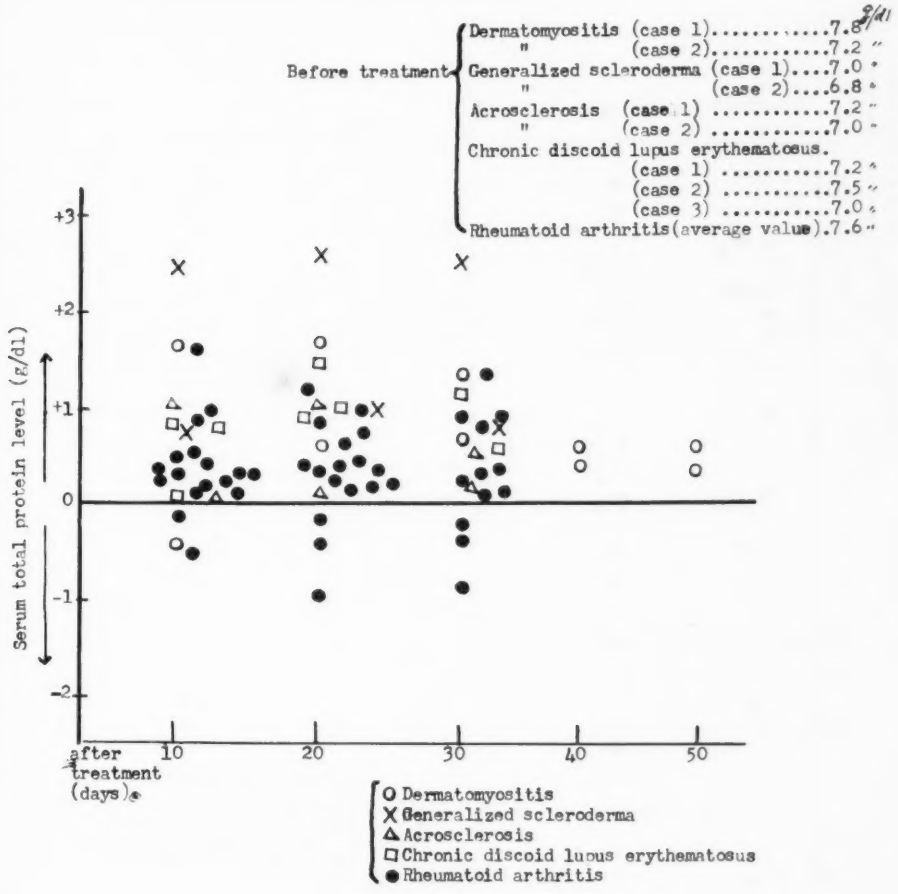

Fig. 1.—Serum protein.

protein level was elevated immediately after this dietary treatment and its elevation was maintained for a month; then the level tended to decrease (Fig. 1).

Albumin-globulin ratio and serum protein fraction (paper electrophoresis [42]) showed no specific changes.

The tyrosine level in serum mucoprotein (Winzler's method [43]) dropped remarkably in all cases (Fig. 2).

Blood Sugar.—Generally, the blood sugar level remained almost constant; however, the level tended to drop in the patients who failed to eat all of the diet.

Liver Function.—This was not disturbed, Takata and Gros reaction and sulfobromophthalein (Bromsulphalein) test revealed no significant change compared with the pretreatment value and tests.

Before treatment:

Dermatomyositis (case 1)	6.0	mg/dl
" (case 2)	10.0	"
Acrosclerosis	7.2	"
Chronic discoid lupus erythematosus (case 1)	5.6	"
Chronic discoid lupus erythematosus (case 2)	7.2	"
Rheumatoid arthritis (average value)	11.4	"

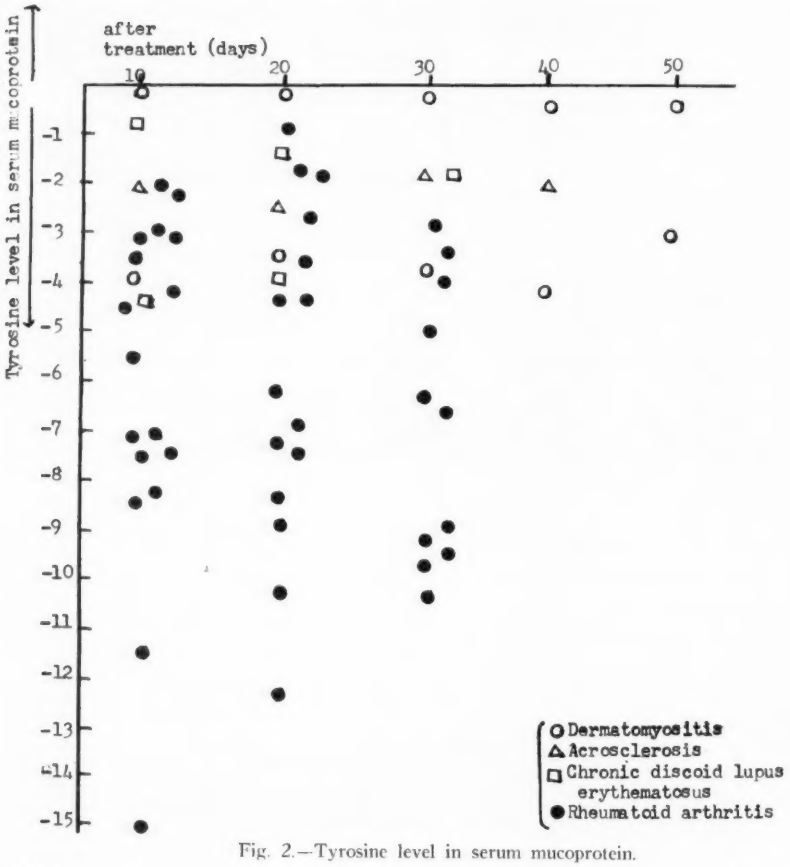

Fig. 2.—Tyrosine level in serum mucoprotein.

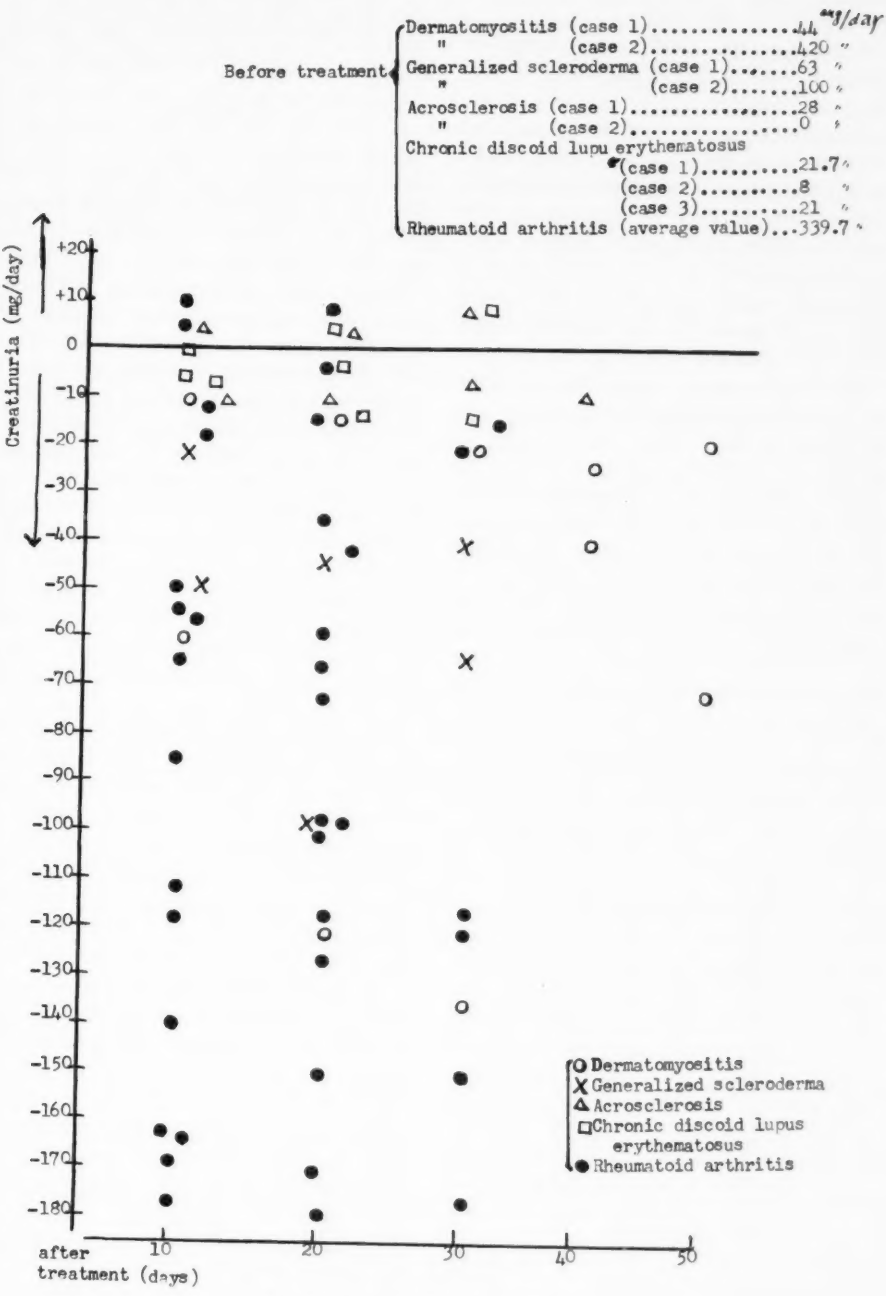

Fig. 3.—Excretion level of creatine.

Epinephrine Test.—The findings were not particularly changed.

Basal Metabolic Rate.[45]—This generally remained unchanged or slightly increased but never dropped.

Urine.—Commonly, protein, sugar, and urobilinogen in the urine were not changed on this diet. However, alimentary glucosuria appeared in two cases of rheumatoid arthritis in three weeks after starting this dietary treatment.

Creatine and creatinine in the urine (Folin's method[44]), in general, were markedly decreased (Fig. 3).

The total nitrogen value in the urine was as follows: Taking the absorption rate of Jellice as 90%; the protein content of Jellice as 83.7%; the protein content of whale, cod, and herring as 20%; its absorption rate over 80%, and the nitrogen value of protein 16%, the daily intake of nitrogen is calculated to be 7.70 gm. in 60 gm. of Jellice and 20 gm. of whale, cod, or herring. The comparison and the balance of the intake and the urinal output of total nitrogen value is in Table 4, which shows that the majority except three cases could be able to maintain positive nitrogen equlibrium.

TABLE 4.—*Excretory Level of Total Nitrogen in the Urine* *

No.	Before Treatment	After Treatment, Days				
		10	20	30	40	50
1	9.80	10.37	10.07	9.07	9.20	9.30
2	5.00	5.00	6.01	5.55		
3						
4	6.01	5.49	6.21	5.34		
5	6.21	4.41	4.49	6.11		
6	6.34	5.70	4.99	5.61		
7	6.468	6.601	6.10			
8	4.202	3.501	4.00	4.401		
	4.91	5.12	4.39	5.11		
10	4.371	5.663	6.024	3.998		
11	5.930	5.136	6.001	5.800		
12	6.615	6.610	6.103	7.240		
13	5.456	5.69	6.001	6.85		
14	6.926	4.999	4.841	4.874		
15	6.926	4.405	4.979	5.496		
16	4.590	5.663	7.248			
17	6.618	4.795	5.705	6.210		
18	6.180	7.140	8.240			
19	4.382	3.101	5.001			
20	8.248	6.146	4.514	5.379		
21	8.730	6.007	7.001	5.772		
22	5.252	4.954	4.914	3.268		
23	7.533	5.970	6.110			
24	8.004	7.820	6.999			
25						
26	8.125	7.49	8.010			

* Grams/day. Daily intake of total nitrogen, 7.7 gm/day.

Comment

This experiment enables us to assume that phenylalanine- and tyrosine-deficient diet can be enforced on collagen disease patients for a sufficiently long period without causing apparent clinical disturbances.

Those, about half the number of the patients, who could not finish the food of an unfamiliar menu were able to eat them all as they grew accustomed to the diet from about the fifth day of the dietary therapy. About half of the patients remarked on the sensation of well-being and lightness of their body as a whole from about the 10th day of the treatment, although there were a few cases which complained of slight general tiredness on the diet.

We assume that this diet is sufficient to maintain the minimum daily requirement of phenylalanine and tyrosine of adults, which is approximately 1.10 gm., calculated by Rose et al.[23]

This dietary therapy resulted in most of the cases in elevation of total serum protein and in only few cases in decrease within 1 gm. per dl. This fact could be interpreted as follows: The serum protein increases, when the phenylalanine intake decreases, as a manifestation of vital reaction to keep the amino acid on a given level necessary for normal metabolism.

As to the total nitrogen value in the urine, as described above, it was decreased in most of the cases, and there was hardly a case which showed a remarkable increase by this dietary therapy.

The nitrogen content of 7.7 gm. in the daily food consisting of 60 gm. of Jellice and 20 gm. of whale, cod, or herring seems to be sufficient to maintain the positive nitrogen balance when it is compared with the urinal nitrogen output, except for the three cases (Cases 1, 18, and 26) as shown in Table 4.

The serum protein fraction was not observed to show any specific alteration, as in improvement of A/G ratio or a decrease of γ-globulin level. Therefore, it seems to imply that dysproteinemia or dysgammaproteinemia advocated by Ehrich[46] as a common denominator of collagen diseases are not etiological factors but only the resultant biochemical variations in the diseases.

As reported by Kelley, Good, and McQuarrie[47] and Kelley, Adams, and Good,[48] the tyrosine level of serum mucoprotein could be a yardstick of rheumatic fever, because its level would be elevated at an acute phase and come down as the clinical symptoms improve by the administration of steroids such as cortisone or corticotropin (ACTH). The authors in accordance found marked decrease of the tyrosine level in the serum mucoprotein in all the cases on this dietary treatment.

It has been commonly recognized that creatine level in the urine of collagen disease patients, especially in generalized scleroderma, dermatomyositis, and rheumatoid arthritis, increases and its level is almost parallel with the degree of condition of these diseases. By this dietary treatment, the creatine level in the urine also decreased in all cases.

Anemia has been said to be one of the important factors for the judgment of prognosis of rheumatoid arthritis and lupus erythematosus. In our dietary treatment no particular changes occurred in the count of red cells, although in one case of rheumatoid arthritis the hemoglobin concentration markedly decreased from 76% to 45% (Sahli) on the 20th day of this dietary treatment.

There were no significant changes in the count of white blood cells.

The erythrocyte sedimentation rate did not show a specific change by this diet, although it tended to decrease in most cases, except for an increase in only one case of rheumatoid arthritis. Improvement of erythrocyte sedimentation rate was assumed to be correlated to that of clinical signs of rheumatoid arthritis.

Blood sugar was found, in all cases, to be constant; alimentary glycosuria was observed in two cases of rheumatoid arthritis in three weeks on the diet, but the blood sugar level remained unchanged.

Proteinuria was not encountered during this dietary therapy.

Through the course of this dietary treatment, the qualitative test for 2,5-dihydroxyphenylpyruvic acid was constantly positive by one dimensional ascending paper chromatography. It is presumed, however, that the excretion of 2,5-dihydroxyphenylpyruvic acid would quantitatively decrease in association with the remarkable decrease of excretion of the intermediary metabolite of phenylalanine as tyrosine, *p*-hydroxyphenylpyruvic acid, and *p*-hydroxyphenyllactic acid.[49]

As stated above, the low phenylalanine and tyrosine diet, we believe, brought about amelioration of patients' subjective complaints, improvement of laboratory data, and also in almost all cases improvement of clinical findings, although it varied from case to case. It indirectly rationalizes the effectiveness of this dietary treatment that cortisone for rheumatoid arthritis, when combined with this diet, is required in only half of the usual dosage and the effect lasts twice as long or more. Therefore, it is desirable to combine this diet therapy with other recognized remedies for the treatment of various collagen diseases. It must be remembered, however, that discontinuation of this diet often reversed the symptoms arrested by the therapy.

As stated above, we have been convinced that low phenylalanine and tyrosine diet results in marked improvement of clinical signs, symptoms, and laboratory data of collagen diseases.

Summary

Low phenylalanine and tyrosine dietary treatment was performed on 26 diffuse collagen disease patients with good results in both clinical signs and laboratory data.

No significant side-effects were observed by a prolonged treatment with this diet, which were convincing of the possibility of continuing the treatment at an individual home.

If the dietary therapy is combined with cortisone for rheumatoid arthritis, half of the usual dosage of cortisone is sufficient and the effect lasts for a longer period.

During this dietary treatment, the qualitative reaction of 2,5-dihydroxyphenylpyruvic acid in the urine was constantly positive by one-dimensional ascending paper chromatography.

We are indebted to Yashiro Kotake, Dean of Wakayama Medical College, and Prof. Ryuzo Iwatsuru for their constant encouragement.

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Reports

Standards and Minimum Requirements for a Dermatologic Service

Recommendations of the American Academy of Dermatology and Syphilology

I. Introduction: The Composition, Educational Functions, Scope, and Responsibilities of the American Academy of Dermatology and Syphilology

The American Academy of Dermatology and Syphilology is the only national society which can be regarded as truly representative of the specialty in the United States. It is the national body in which all those who have qualified as specialists by receiving the Certificate of The American Board of Dermatology are eligible for Fellowship.

While the general purpose of the Academy is educational, it is obvious that the education of physicians in the specialty is, to a great measure, dependent upon the opportunities and facilities, the equipment and standards for investigation, diagnosis and patient care, which are available to the services of dermatology in the hospitals and training institutions throughout the country. It is in these institutions that medical students, interns, residents, and other physicians will inevitably receive their major instruction in the specialty and their impressions of its worth and potentialities. Moreover, such institutions sometimes also participate in or organize programs for the continuing, or postgraduate education of the specialist.

Because the American Academy of Dermatology and Syphilology is a national society which represents all qualified members of its specialty and because its fundamental objectives are to maintain and/or improve the continuing education of physicians in dermatology and syphilology the Academy feels that it is within its sphere of activity to formulate, foster, and assist with the maintenance of proper standards for personnel and facilities in the specialty in our hospitals and teaching institutions, both civil and military.

The following outline of standards, requirements, and practices is submitted as a guide for establishing and maintaining maximum dermatologic efficiency in institutional practice. Obviously, all standards, requirements, and practices so set forth cannot apply in every detail to each hospital or training service, but they should be applicable to the larger ones and especially to those associated with medical schools and/or residency-training programs.

Submitted for publication March 20, 1959.

II. Recommended Organizational Structure for a Service of Dermatology in a Teaching Hospital

Dermatology is unique among the medical specialties in the number and diversity of its essential diagnostic, investigative and therapeutic techniques and modalities. Perhaps this is one reason why it appears to transgress into fields which other specialties consider their special domain. At times dermatologic problems may appear to overlap with those of the plastic surgeon, internist, radiologist, pediatrician, allergist, pathologist, microbiologist, biochemist, and physical therapist; etc. Since a dermatologic diplomate has qualified as expert, both by training and experience, to use these many diverse approaches in the study, diagnosis, and management of diseases and changes of the skin and its appendages, it is to the best interest of the patient afflicted with a dermatosis that he receive unhampered expert dermatologic diagnosis and management whenever feasible. Furthermore, because of the breadth and the scope of the many approaches used in dermatology it is often also to the best interest of the patient, as well as good teaching and research, that dermatology have departmental status rather than function as a division of internal medicine. It is desirable that the director should have free access to administrative authority without reference to other directors of services and should exercise sole professional control within his service. He should represent his service at all appropriate committee and board meetings when deliberations of these bodies are concerned with professional and educational dermatologic matters. In an institution either seeking or holding approval for a residency training program in dermatology and

syphilology, the director of dermatology should determine the training program to be followed by the trainees in the specialty, as well as choose the faculty.

In order to carry out effectively its functions in a "teaching hospital," the service of dermatology needs and should have the facilities and equipment set forth in the following paragraph.

III. Recommended Physical Facilities and Equipment for a Service of Dermatology in a Teaching Hospital

The service of dermatology should have all necessary apparatus and physical facilities within its own department because it is only under these circumstances that it can effectively fulfill its functions both in the care of patients and in the teaching of medical students, interns, and residents. For example, it is uneconomical and inefficient to refer dermatologic patients to another division of the hospital for radiation therapy, and, furthermore, by reason of experience and training, the dermatologist is the specialist best qualified to use this therapeutic modality in the management of skin diseases. Biopsies and surgical excision of skin lesions require rooms equipped for minor surgery within the service of dermatology. Also, dermatologists require microscopes, appropriate culture media, and other laboratory facilities within their own service; these requirements are in addition to those provided centrally. As a minimum, the specialized laboratory procedures which should be done within the geographical confines of his service and under the direction of the dermatologist, include the examination of potassium hydroxide preparations, mycologic cultures, preparation and staining of Tzanck smears, and dark-field examinations. If tissue sections are cut and stained in the central laboratory, additional slides should be made and sent to the service of dermatology so that they are available for study by the staff and residents; in larger services of dermatology, it is often both advisable and feasible for the sections to be cut and processed in the laboratories of the dermatologic service. *The availability of these treatment and laboratory facilities in the service of dermatology and under the direct control of the dermatologist is essential for the best care of patients and for an adequate graduate teaching and research program.*

Although outpatients constitute the largest part of dermatologic hospital practice, it is essential also that adequate space for inpatients be provided, and it is self-evident that these patients should be on the dermatology service and under the direct control of the dermatologic staff.

Wherever dermatologic training is conducted, it is highly desirable and almost essential to make provisions for a basic dermatologic departmental library within the geographical confines of the service. This makes it possible for both members of the staff and residents to refer frequently to dermatologic books and journals during the course of the day. The teaching value of a resident's systematic and unhampered reading and reference to several textbooks and/or pertinent articles in journals (especially just after he has examined a patient and before discussing the case with a consultant) cannot be overemphasized. Obviously, this is not feasible if he finds it necessary to leave the department in order to consult reference texts and journals maintained in a medical library in another (and sometimes distant) part of the institution.

IV. Recommended Scope of the Dermatologic Service in a Teaching Hospital

The service of dermatology and syphilology should provide and coordinate actions relative to the examination, diagnosis, care, treatment, and appropriate disposition of patients afflicted with diseases of the skin, including diseases with significant cutaneous manifestations and those which additionally involve the mucous membranes, as well as those which have systemic manifestations. It should perform these functions for both inpatients and outpatients. Where such diseases are found to have components which require general medical or other specialistic skill, the service of dermatology and syphilology should consult with all other services, as may be appropriate, but it should be responsible for establishing the correct diagnosis, including those arrived at histopathologically, and for the management of the patient.

V. Recommended Personnel for a Service of Dermatology in a Teaching Hospital

The Chief of Service and the physicians of his staff should be certified or be eligible for a certification by the American Board of Dermatology.

In military service, a nondermatologist should not be assigned to the dermatologic service without his consent; also, a member of the dermatologic staff should not be assigned to another service or another department without his consent, unless, of course, the exigencies of war or other circumstances make it mandatory. Furthermore, wherever approved training is conducted, it is desirable for residents to devote their full time to dermatology, except for assignments which in the opinion of the director of dermatology, contribute to their training. In many instances, cooperative training efforts with other departments, (such as those of microbiology, pathology, biochemistry, internal medicine, allergy and im-

munology, radiology, and plastic surgery) are feasible and often desirable.

VI. Professional Practices Review Council

In view of the fluid state of medical practice, in which dermatology participates no less than any other specialty, the American Academy of Dermatology and Syphilology has appointed a Committee on Standards for the establishment of standards and the review of professional practices in order that the recommendations and requirements contained herein will be subject to continual revision, consistent with current progress. Whenever necessary, the Committee on Standards of the American Academy of Dermatology and Syphilology may consult and cooperate with other medical advisory bodies, such as the Council on Education and Hospitals of the American Medical Association, the American Board of Dermatology, Inc., the Joint Commission on Hospital Accreditation, and the Residency Review Committee for Dermatology. Directors of dermatologic services who are members of the Academy should be invited to present to the Committee on Standards, in writing, their problems of professional practice, teaching, residency training, facilities, or recommendations for changes, so that the committee can act, direct, or advise as they deem proper in each instance.

Respectfully submitted by the Committee on Standards of the American Academy of Dermatology and Syphilology:

MARION B. SULZBERGER, M.D., Chairman
MARCUS R. CARO, M.D.
EDWARD P. CAWLEY, M.D.
ARTHUR C. CURTIS, M.D.
CLARENCE S. LIVINGOOD, M.D.
FRANCIS W. LYNCH, M.D.

Mayo Clinic.

A Curious Foreign-Body Tumor

JOSEPH V. KLAUDER, M.D., Philadelphia

When first seen, the patient, a man, age 65, presented a node on the dorsum of the right hand. It was firm, circumscribed 1 cm. in diameter and raised about 0.75 cm. Its surface was crusted. It appeared 18 months previously, when he was in Japan. He thought it was caused by the bite of an insect. About one year later it was excised; the site never healed. The lesion gradually returned to its former state.

Although it resembled acanthoma, it was not clearly such a lesion; nor was it regarded as a keratotic nodule, epithelioma, or molluscum contagiosum. Since the patient stated that at times there was a discharge of pus, a low-grade pyogenic infection was suggested. Accordingly, a wet dressing of an antiseptic solution and neomycin ointment was prescribed.

When seen again, the top of the lesion was macerated; when the surface was rubbed with a wet cotton pledget, a rod-shaped metallic piece was dislodged, 3 mm. long and about 1 mm. in diameter. Several days later the patient removed another similar metallic rod. A roentgenogram was then made; the report was: "There is a metallic foreign body approximately 1×5 mm. in the skin of dorsum of right hand corresponding to the area of ulceration. There are no complicating pathologic changes in the underlying bone structure." When the lesion was curretted, this third metallic rod was removed. Subsequently, the lesion disappeared.

The figure is a photograph of the lesion after removal of the second foreign body. At this time the lesion was smaller than when first seen.

Histopathologic Examination *

This specimen is not characterized by any specific change. There is hyperkeratosis, hypergranulosis, and acanthosis with intra- and intercellular edema. In the dermis, there is basophilic degeneration of the collagen in the upper three-fifths of the dermis. The basophilic degeneration is more pronounced and localized at one end of the sections. There is a diffusely distributed lymphocytic infiltrate throughout the dermis. At one area, the infiltrate is more intense. There are increased fibroblasts in the lower part of the dermis. Examination with polarized light failed to detect birefringent material in the tissue. The picture is epidermal hyperplasia and mild inflammation in skin from exposed surface.

The patient is a metallurgic engineer, engaged in the manufacturing of metallurgic equipment. His laboratory identified the metallic pieces as 70% zinc and 30% copper (ordinary brass). Such

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* Dr. Herman Beerman.

Lesion on dorsum of hand after removal of the second brass rod. At this time it was smaller than when first seen.

material is not used in his plant but is in plants that he visits in this and foreign countries. He was on such a visit in Japan when, as mentioned, the lesion on his hand first appeared.

He had no knowledge of how the brass rods penetrated his skin. He denied any injury of the hand. He stated he does not handle any metallic material. His work is entirely executive (as president of his company). He does not handle, repair, or inspect any equipment that he manufactures in his own plant, or other plants that he visits. He has no hobbies and no work shop in his home.

There was no evidence or history of lapses of consciousness, alcoholism, or reason to suspect malingering or to suspect a factitial lesion.

Detailed questioning regarding time and place that he thought he was bitten by an insect; the information was elicited that he only presumed he was bitten. He had no knowledge of toy pistols in Japan that may have "shot" brass plugs. He had no knowledge of any equipment that ran afoul, projecting the brass pieces. There are no high-pressure projectors in his plant or those that he visits. His plant employs ultrasound to clean metals. He could not conceive how the brass rods could penetrate his skin through that medium.

Since these Sherlockian considerations gave negative response, the mystery of the three little brass rods remained unsolved.

1934 Spruce St. (3).

Antimycotic Cream and Powder

Clinical Evaluation

EUGENE S. BERESTON, M.D., D.Sc. (Med.), Baltimore, Md.

Certain saturated and unsaturated fatty acids are reported to have antifungal activity.[1,2] Of these, undecylenic acid and its zinc salt have been used most widely in this field. The effectiveness of undecylenic acid preparations is limited in those cases where increased penetration and keratolytic action are required. In an attempt to find a compound which meets these additional requirements, sulfur and pelargonic acid were combined. Sulfur has been extensively used as a "fungicidal" and keratolytic agent for many years, but its chemical behavior with unsaturated fatty acids prevents its combination with undecylenic acid. The saturated nine-carbon fatty acid, pelargonic acid,[1-3] whose antifungal activity equals that of undecylenic acid, was combined with sulfur because reactivity is not a problem with this combination.

The sulfur (Thylox) was a fine-particle (1μ-3μ) highly reactive material obtained from coal-gas purification. It has demonstrated its advantages in preparations, such as soap and acne medications.

Two formulations were developed: One was a cream containing pelargonic acid 4%, zinc pelargonate 10%, and the fine-particle sulfur 2% in a

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Furnished by Shulton, Inc., Clifton, N. J.

From the Division of Dermatology, University of Maryland School of Medicine.

Results of Study

Infection	Causative Organism *	Cases, No.	Cures	Average Time, Wk.	Relapses
Tinea capitis	M. audouini	21	0	--	0
	M. canis	2	2	6	0
Tinea cruris	E. floccosum	17	17	2	2
	T. mentagrophytes	5	2	3	0
	KOH positive, culture negative	7	4	2	1
Tinea pedis	T. mentagrophytes	151	139	3	12
	T. rubrum	29	19	6	7
	C. albicans	3	3	3	0
Vulvitis	C. albicans	14	5	2	0 (irritation in 1 case)
Tinea corporis	T. rubrum	20	12	8	5
	T. mentagrophytes	4	4	3	0
	M. canis	3	3	2	0
	M. audouini	5	5	3	1

* M. indicates Microsporum; E., Epidermophyton; T., Trichophyton.

vanishing cream base, and the other, a powder containing pelargonic acid 2.5%, zinc pelargonate 20%, and zinc sulfide 3% in a talc base.

These formulations were studied for nearly two years in 281 patients with all types of superficial fungus infections. The laboratory work consisted of direct microscopic examinations in potassium hydroxide and cultures on Mycosal agar.

Patients were instructed to apply the cream to the affected areas morning and night. The powder was used in tinea pedis as adjunctive treatment with the cream. The Table presents the results of the study.

Comment

In tinea cruris, tinea pedis, and tinea corporis, treatment with this antimycotic cream and powder has produced satisfactory results. In Trichophyton rubrum infections, the improvement rate and relapse rate were higher than for infections due to other organisms. In tinea capitis due to Microsporum audouini, results have been unsatisfactory. In onychomycosis the results have also been unsatisfactory.

Summary

An antifungal cream (containing a fine-particle sulfur, pelargonic acid, and zinc pelargonate) and an antifungal powder (containing pelargonic acid, zinc pelargonate, and zinc sulfide) were found to be highly efficacious in the treatment of tinea cruris, tinea pedis, tinea corporis, and superficial moniliasis. It proved to be unsatisfactory in tinea capitis due to Microsporum audouini and onychomycosis. In Trichophyton rubrum infections, initial results were good but the relapse rate was high.

Irritation from these antifungal agents was observed only on mucosal surfaces. No other adverse reactions were observed.

The antimycotic preparations used appear to be satisfactory therapeutic agents in the treatment of certain superficial fungus infections.

University of Maryland School of Medicine (1).

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ANNOUNCEMENTS

Seminar on Dermatopathology.—The University of Texas Postgraduate School of Medicine will present a seminar on Dermatopathology on Nov. 12, 1959, in the auditorium of The University of Texas M. D. Anderson Hospital and Tumor Institute. This seminar is designed for pathologists and dermatologists. It will be built around sets of slides which will be mailed to the participants in advance for individual study and diagnosis. Dr. Elson B. Helwig and Dr. J. Leslie Smith will act as moderators for the presentation of the cases and the discussion.

Registration will be closed Oct. 12, 1959.

Although not a part of the Fourth Annual Clinical Conference scheduled for Nov. 13 and 14, 1959, this seminar has been scheduled to precede immediately the Clinical Symposium because of the areas of overlapping interest.

For further details, write the Office of the Dean, The University of Texas Postgraduate School of Medicine, 410 Jesse Jones Library Building, Texas Medical Center, Houston 25, Texas.

Conference on Clinical Anticancer Drug Research.—The U.S. Public Health Service Cancer Chemotherapy National Service Center will hold a two-day conference on clinical anticancer drug research in Washington, D.C., on Nov. 11-12, 1959.

The meeting will be held at the Hotel Statler.

The principal subject under discussion will be the clinical research being carried out as part of the program of the Cancer Chemotherapy National Service Center. In addition, speakers have been invited to present papers on other phases of the chemotherapy program, such as screening for anticancer activity, synthesis and pharmacology of potential anticancer agents, radiation and surgery as adjuvants to chemotherapy, and anticancer drug research abroad.

Dr. B. H. Morrison III, of the Service Center staff, National Cancer Institute, Bethesda 14, Md., is in charge of arrangements for the conference.

The New, Newer, and Newest

Why are the Proceedings from some societies uniformly good and interesting to read while those from other societies are too often uninteresting? Some of the better Proceedings, you will note, come from societies that have Recorders who are elected or appointed, not yearly, but for a period of years. They are usually persons of stature whose judgment on what to delete and include is respected by the membership, and the result is usually a good tight report containing only meaningful laboratory reports, descriptions, and comments. It should be recognized that cases that are worth seeing and discussing are not always suitable for publishing; they may be too familiar or they are "show cases" which, of course, should be reported by title only for their statistical and reference value; besides, it distinguishes the workers from the shirkers. Some societies employ professional reporters to untangle the all-too-frequent garbled comments—so few of us are able to speak ad-lib in language suitable for publication. In such cases, discussors should be given the opportunity to approve of their edited remarks. Young men, we are told, consider the Proceedings invaluable, and the ARCHIVES, therefore, will soon devote more pages to them. To keep them current, Proceedings should reach the ARCHIVE's office not later than two or three months after the meeting, since it takes five to six months to transfer them to the printed page. The inclusion of suitable illustrations would enhance their value too, but most important, it is careful, skillful screening and editing by one who attended the meeting to make certain of outstanding Proceedings.

Larry Beinhauer wants it known that he has resigned from the Advisory Committee to the National Foundation for Research in Cutaneous Medicine, Inc.

Irvin Blank, Associate in Dermatology at Harvard, received the Special Award of 1959 by the Society of Cosmetic Chemists. The title of his paper was "Water on Troubled Skins—Oil on Troubled Waters." Irvin is the Blank who prefers water!

Herbert A. Luscombe has been appointed Professor of Dermatology at the Jefferson Medical College and is the newly-elected President of the Philadelphia Dermatological Society; Walter Shelley is Secretary.

In New York, Herbert Spoor is now President and John H. Meyers, Secretary, of the Metropolitan Dermatological Society. The New Jersey Dermatological Society, John R. Tobey, President, and Hugh McCulloch, Corresponding Secretary. The New England Dermatological Society—Joseph Goodman, President, and Robert Tilley, Secretary, and for the Rhode Island Dermatological Society, Bencel Schiff, President, and Louis Levine, Secretary.

The Forty-fourth Scientific Assembly of the Interstate Postgraduate Medical Association, Nov. 2-5, Chicago, will be addressed by Theo Cornbleet, Joseph Forbrich, Paul Lazar, Cleveland White, and Samuel Zakon.

A little late in the year and untried by us as yet, we pass this on as our public service bit—advice published in a recent *New York State Journal of Medicine*.

"When an apparently hostile bee is encountered, one should not move rapidly. The eyes should be slowly covered to avoid attracting attention to their movement or a prone position should be assumed with the face hidden. A hasty retreat should be made only when a whole nest or hive of stinging insects is disturbed."

H.R.

Society Transactions

CLEVELAND DERMATOLOGICAL SOCIETY

Frank M. McDonald, M.D., President
Harold N. Cole Jr., M.D., Secretary
John A. Kenney Jr., M.D., Reporter

Sept. 18, 1958

I. Autoerythrocyte Sensitization. Presented by DR. R. C. GRIGGS and DR. W. F. DOWDELL (by invitation).

A 39-year-old housewife had recurrent episodes of purpura since 1953. These started after an apparently routine appendectomy. The lesions are characterized by the following course: She first notices a tingling sensation in an area of her skin; within 24 hours there appears an erythematous, slightly raised area, which rapidly becomes purpuric and usually rather painful. These areas often occur at the time of menstruation and on all areas of the trunk and extremities, primarily the upper legs.

In association with these lesions she has frequently had abdominal pain, hematuria, intestinal obstruction, melena, and, recently, periods of unconsciousness.

During the time of exacerbation there are numerous purpuric areas on the legs, varying from 1 to 10 cm. in diameter, often with a clear center.

Repeated blood cell counts, platelet counts, and blood-clotting studies have been normal; tourniquet test, positive.

The skin biopsy specimen and abdominal exploration with intestinal biopsy specimen have revealed only extravasated blood.

The patient has been on steroid therapy for several months, with moderate improvement.

Discussion

DR. R. C. GRIGGS: This patient has been bothered by purpura for the past five years, primarily of the upper legs, although she gets it in other areas and also in other organs of her body. The main difference between this and some other types of purpura is the peculiar sensitization she exhibits. She first notices a tingling sensation in an area of skin, which becomes very painful after the purpura appears.

DR. R. C. GRIGGS: We believe her purpura is due partly to sensitivity to her own red cell stroma. She gets allergic reactions to this material. I think the best thing to do to illustrate this is to show some of the slides. What we did with her and with a normal person was to take 0.1 cc. of blood from a vein and inject it without any anticoagulant intracutaneously; on this slide you see the kind of reaction 24 hours later in a normal person; 0.1 cc. of saline was injected into the skin on the other arm. We have done this in a number of people with purpura of various kinds and have gotten entirely negative reactions, except in this woman. Here is the initial type of reaction she gets. This is an indurated wheal on her left forearm. There is no reaction to the injection of saline on this side. We must be careful not to nick a blood vessel or we will get a false-positive reaction. This slide shows a large wheal, with beginning development of purpura surrounding it. This is 24 hours after the initial injection. You can see the saline injection at this site. These other spots are spontaneous lesions.

This phenomenon has been described primarily by Dr. Gardner and Dr. Diamond, who reported this syndrome in *Blood* (10:675 [July] 1955). At that time they reported on four such cases, and since that time they have had five others, all women. On going into the history of each case, the onset was shortly after some traumatizing episode. Ours is the only one which started after surgery. One of their patients dropped a window on both hands and for 12 years after that had recurrent episodes of purpura. One patient was in an automobile accident and received several fractures, with the development of large hematomas. In another report, a Navy Wave developed hers at a time when she was receiving many inoculations; each time she got larger hematomas, and she finally developed this syndrome. (Gottlieb and his associates, *Am. J. Med. Sc.* 233:196 [Feb.] 1957.) It has been demonstrated by a little more refined method that the patients are sensitive to the red cell stroma. If you wash the red cell as free as possible and inject it, it will produce this reaction. The hemoglobin alone and serum proteins do not produce the reaction.

Our patient has had other symptoms, mainly recurrent gross hematuria and gastrointestinal bleeding on several occasions, and she has been

Submitted for publication July 2, 1959.

very ill with intestinal obstruction lasting about 10 days; when it subsides she has several days of melena. At one time she had an abdominal exploration and a biopsy of the intestine, which showed hemorrhagic areas like those found in Henoch's purpura, where there was a constricting band around the small intestine. In the past few months she has had several episodes of unconsciousness. Repeated lumbar punctures have all been negative. This has been noticed in others with this syndrome, and it is thought to be due to some type of bleeding or reaction in the central nervous system. She has had severe episodes of abdominal pain. Many patients with this syndrome have left-upper-quadrant pain, and because of this patients have had their spleens removed, without any appreciable change in the course.

There is no good therapy for this condition at this time. Splenectomy has been tried, without benefit. A number of patients have been tried on courses of desensitization. All this apparently does is make the patients worse. Even very minute doses of red cell stroma will bring on a full-blown picture. All attempts have led to abandoning this method of therapy. Our patient's symptoms are related primarily to her menstrual periods, although she is between menstrual periods now and she has purpura on her skin all the time. Artificial menopause has been produced in other patients, without any change in the course. This woman's history gives a closer relationship between the menstrual cycle and the purpura than others. At the present time we have been trying steroid therapy. She has been on Meticorten since May, in decreasing dosages. She is now on 15 mg. a day and is having no side-effects from it, and ever since she has been on it she has had no episodes of unconsciousness, gastrointestinal bleeding, or hematuria. She has continued to have the skin lesions, however. She feels very much improved. We have not retested her to see if her sensitivity to red cells is still present. The only other encouraging thing about this syndrome is that most of the patients over a period of years seem to have less and less trouble. None has died so far, and apparently after 10 or 15 years they have no more symptoms or only have them occasionally. At the present time we do not know what is causing this reaction or how she became sensitive, but I think it is certainly an interesting type of nonthrombocytopenic purpura.

Someone asked the patient's response to surgery. She had an extensive exploration. The gallbladder and spleen were inspected, and a biopsy of the intestinal wall was done; she withstood this very well.

DR. E. W. NETHERTON: I should like to know the sex incidence in the other cases that have been observed.

DR. R. C. GRIGGS: They were all in females.

DR. E. W. NETHERTON: Have they followed trauma or any operative procedure in every case? Another question I have is whether this patient developed it right after her operation and whether she had antibiotics postoperatively? Did they think that any procedure carried on at the time of surgery might have brought this on?

DR. R. C. GRIGGS: There have now been 12 or 13 cases that I know of. There have been four women, including this one in Cleveland, who are not reported in the literature, and nine in the literature, and all of them have followed some kind of trauma, operative trauma or some type of accident with large hematoma formation. This patient's surgery was done in May or June, 1953. In August of that year, following her menstrual period, she first had this difficulty. I do not know anything about the surgery and the doctor who is caring for her now was not taking care of her at that time. We cannot obtain the operative report, so we do not know anything about the procedure. As far as we can tell from talking with her and with her husband, it was not unusually traumatic in any way.

II. Xanthoma Tuberosum. Presented by DR. B. K. DAS, DR. D. E. SEVASTIANOS, and DR. M. M. JALLAD.

A 47-year-old white man was first seen in the dermatology outpatient department on May 29, 1958, with nodules of 12 years' duration on both elbows and the left knee. He saw his private physician in 1952 for this complaint and was treated with ointment, with no benefit.

The patient is a musician by profession, a violinist.

He has a brother with eczema. His mother died of leukemia in 1952. His sister and father both have diabetes. He has one daughter who is apparently well. The father's cholesterol on Sept. 11, 1958, was 182 mg.

The patient has yellowish, waxy nodules on the elbows and left knee. The nodules are largest on the elbows, some 3 to 4 cm. in diameter. All other systems are essentially normal. The patient has exogenous obesity.

STS was negative on May 29, 1958; postprandial blood sugar, 110 mg. % on June 3, 1958; glucose tolerance test (oxytocic curve), return to 90 mg. % in two hours on June 25, 1958; hemogram and urinalysis within normal limits on Aug. 5, 1958; cholesterol, June 3, 1958, 422 mg. and Sept. 11, 1958, 288 mg. On Sept. 19, 1958, blood was sent to Dr. Helen Brown, Cleveland Clinic, for special analysis: free cholesterol 140, cholesterol esters 253, lipid phosphorus 212, neutral fat not obtained. Total lipid will be in excess of 1,100. Electrocardiogram on May 29, 1958, showed nonspecific changes.

X-rays taken on Oct. 28, 1958: chest, no evidence of pathologic process in the chest; gallbladder series after Telepaque, excellent filling and emptying following the fatty meal, no stone.

Biopsy report: The section shows moderate hyperkeratosis with loosely woven strands. There is some follicular plugging. The epidermis is otherwise not remarkable. A uniform infiltrate occupies all but the papillary portion of the dermis. Conspicuous in the infiltrate are the large macrophages. Fat stains are requested.

III. Pseudoxanthoma Elasticum; Rosacea; Xanthelasma. Presented by DR. B. K. DAS, DR. D. E. SEVASTIANOS, and DR. M. M. JALLAD.

A 69-year-old white woman was seen in the dermatology outpatient department on May 1, 1958, for an eruption on the sides of the neck and both arms. The eruption had been present for several years.

The patient has been in various departments at Cleveland Metropolitan General Hospital with hypertensive cardiovascular disease, minimal bronchiectasis, Parkinsonism, chronic dacrocystitis, and mastoiditis.

The patient has a yellowish, waxy, papular eruption on the sides of the neck and volar surface of both arms, extending from the middle of the arm to the middle of the forearm. No other areas of the body are involved. Erythematous papules are seen on the face, particularly in the flush area. Ophthalmologic consultation was held and no angioid streaks were seen.

The clinical blood cell count was within normal limits. Urinalysis was within normal limits. Total cholesterol, May 25, 1958, 263 mg.; Sept. 17, 1958, 223 mg. X-ray of the chest on Jan. 24, 1958, was reported as showing chronic pulmonary emphysema. On Aug. 8, 1958, a chest film showed minimal to moderate cardiac enlargement and bronchiectasis of the basilar lung fields.

A biopsy report on May 21, 1958, showed slight hyperkeratosis, and the rete pegs were flattened for the most part. The underlying dermis close to the epidermis was pale and eosinophilic. Elastic tissue stains revealed clumping of the elastic fibers in the lower portion of the dermis.

Discussion

DR. GEORGE J. GABUZDA: Patients may present with the problem of cutaneous xanthomata. Since I know relatively little about the dermatologic diagnosis of the various xanthomata, I hope to present to you some metabolic aspects that might be of interest. Of course, one must first consider whether the xanthomata are primary or are secondary to some other generalized disturbance of lipid metabolism, such as that associated with diabetes or biliary cirrhosis. I presume that here we are dealing with a primary abnormality that is in some way related to the metabolism of lipids. A rational approach to management of these patients must take into consideration several recent advances of interest. The first of these involves recent work concerning the synthesis of cholesterol. First, I should point out that the level of cholesterol in the blood does not have the relationship to dietary cholesterol that had been presumed for many years. Although the biochemistry involved is complex, the final conclusion can be quite simply stated as follows: Cholesterol can be synthesized quite readily in various animal species, including man, from relatively simple, readily available biochemical precursors, such as acetate. Various fatty acid derivatives can be broken down into simple two carbon fragments. These fragments are eventually condensed in units of six carbon chains to form a compound identified as squalene. Subsequently, a ring compound is formed to synthesize a cholesterol molecule. This synthesis of cholesterol from acetate by way of the intermediate squalene is now very well established.

Another important point that must be considered in discussing xanthomata is whether the basic problem involves primarily an excess of cholesterol which becomes deposited in cells or whether the basic problem involves primarily a defect at the cell level which accounts for abnormal lipid metabolism. This important question, to my knowledge, has not been answered. If the former situation applies, one might expect benefit from measures taken to control the availability of cholesterol precursors; if the latter applies, obviously relatively little can be accomplished until the cellular defect is elaborated. It would seem very probable that some cellular abnormality is involved.

The management of patients with xanthomata must take into account at least these two concepts. If a cellular defect is involved there is obviously very little that can be done about it until its nature is defined. The only other alternative is to direct attention toward decreasing the availability of various precursors of cholesterol, since it is known that abnormal levels of lipids in the blood can be modified by dietary manipulation. This brings us to a consideration of some recent information regarding the effect of dietary factors upon blood lipids, including cholesterol, in man. Dietary cholesterol level per se has practically no influence upon the level of cholesterol in the blood. Recent information indicates that the fat content of the diet influences blood cholesterol level to a greater extent. There are data, for instance, to show that people living in parts of the world where fat is used sparsely have lower cholesterol levels than do people who live in parts of the world where fats are used freely, for example, in the United

States and in Scandinavian countries. In addition to the total amount of fat in the diet, the kind of fat also has some bearing on this matter. In general, vegetable fats tend to be associated with lower blood cholesterol levels and animal fats with higher blood cholesterol levels. Thus, dietary management of patients must take into account not only the total amount of fat in the diet but the type of fat involved. The diet, therefore, should be restricted in fat content and especially in fat of animal origin. This type of regimen would then be hypocholesteremic.

Another approach to the problem of abnormal lipids in the blood has been to administer agents which prevent the absorption of dietary cholesterol. One such agent is sitosterol. If the observations that dietary cholesterol has relatively little, if anything, to do with blood cholesterol level are correct, it would seem unlikely that the use of a compound directed at decreasing the absorption of cholesterol should be expected to have a beneficial effect. Because of the relation of hypercholesteremia with hypothyroidism and decreased blood cholesterol level with hyperthyroidism, thyroid hormone has also been used therapeutically in an attempt to reduce blood cholesterol level. It does not seem to me that this type of therapy is directed at the basic problem in patients with xanthomata.

It would seem that until more knowledge is gained concerning the basic problems involved in xanthomata, we can hardly expect to provide definitive treatment. In the meantime, it would seem logical to attempt to control the condition by prescribing a diet reduced in fat content and containing vegetable fat in preference to animal fat. There seems to be less rationale for restricting dietary cholesterol or for using agents which interfere with the absorption of cholesterol.

DR. GEORGE H. CURTIS: The first patient, Case 2, has typical lesions of xanthoma tuberosum. There is no family history of xanthoma, except possibly in his father, whose blood cholesterol was within normal limits. There is no clinical evidence of arterial or of heart disease in the patient, and he leads a fairly active life. The condition in the patient must at present be included among the essential familial xanthomatoses of Thannhauser's classification, since he presents no evidence of liver disease or hypothyroidism. In the other xanthomatoses among the group of hypercholesteremic xanthomas, I have seen only one that followed thyroidectomy for hyperthyroidism. The papular xanthomas were widely distributed but concentrated about the elbows and knees. The patient had had a low basal metabolic rate with moderately increased blood cholesterol. Those factors, including the skin lesions, disappeared upon administration of dessicated thyroid.

A group in our Research Division (Cleveland Clinic) has been working on the problem of dietary control of the hypercholesteremias. Many palatable diets, chiefly vegetable-fat diets and low-animal-fat diets, have been devised. However, not too much success has been obtained with dietary management, although high cholesterol levels have been decreased, but never much below 300 mg. per 100 ml. of blood. The diets have not had any effect upon the skin lesions. The diets are relatively expensive, and this patient states he has been unable to afford the low-fat diets. He had tried a low-animal-fat diet, along with one of the cholesteremic reducing drugs, for a short time and thought the skin lesions had been reduced somewhat. Our Research Group has been conducting a clinical investigation with Benzmalocene and diets but with unimpressive results so far.

As for the case of pseudoxanthoma elasticum, Case 3, I believe it is typical. The patient presents the papular lesions, which at this time are not dense enough to form plaques and the cutis laxa type of change in the skin. On the neck, abdomen, and in other sites of predilection, the lesions are typical. Apropos to this condition, there are two recent papers by Shaffer, Copelan, and Beerman (Pseudoxanthoma Elasticum: Cutaneous Manifestation of Systemic Disease; Report of a Case of Paget's Disease and a Case of Calcinosis with Arteriosclerosis as Manifestations of This Syndrome, A. M. A. ARCH. DERMAT 76:622-633 [Nov.] 1957) and one by Loria et al. (Pseudoxanthoma Elasticum [Grönblad-Strindberg Syndrome]: Clinical, Light and Electron Microscopic Study, A. M. A. ARCH. DERMAT. 76:608-618 [Nov.] 1957), in which the condition is discussed from the standpoint of a systemic disease rather than one limited to the elastic tissue of the skin. Apparently, this disease belongs among the inherited and congenital diseases but may appear at any time, usually early in life. The elastic tissues of other systems are involved, such as in the cardiovascular system, thyroid, etc. In one case there was an associated Paget's disease; in another calcinosis and arteriosclerosis were associated. In still another patient there was an associated peptic ulcer but after gastrectomy histologic examinations showed no changes in the elastic tissues of the stomach. I thought the histologic sections in this case were typical.

DR. RUTH RAUSCHKOLB: We have for your perusal today some of the results we got from the Cleveland Clinic from Dr. Helen Brown. This man is definitely going to be hyperlipemic. His total lipid is going to be in excess of 1,100, and natural fat has not been added to that yet. Dr. Brown felt from past experience with 34 cases that this man might have some reasonable hope of improvement on a low fat diet. If you give it all in one meal, he will be much happier, because he can take two meals with no fat if he knows he will have one good meal.

IV. Calcinosis Cutis with Ulceration of Leg and Venous Insufficiency. Nephrolithiasis with Soft Tissue Calcification. Diabetes Mellitus (Recent). Presented by Dr. B. K. Das, Dr. D. E. Sevastianos, and Dr. M. M. Jallad.

V. Urticaria Pigmentosa. Presented by Dr. Allen E. Walker and Dr. John J. Stewart.

VI. Urticaria Pigmentosa. Presented by Dr. Allen E. Walker and Dr. John J. Stewart.

VII. Lupus Vulgaris. Basal-Cell Epithelioma (Remote). Presented by Dr. Allen E. Walker and Dr. John J. Stewart.

VIII. Scleroderma. Presented by Dr. B. K. Das, Dr. D. E. Sevastianos, and Dr. M. M. Jallad.

IX. Aeroselerosis. Presented by Dr. Allen E. Walker and Dr. John J. Stewart.

X. Vitiligo. Presented by Dr. Ruth R. Rauschkolb.

XI. Vitiligo. Presented by Dr. Ruth R. Rauschkolb.

XII. Porokeratosis Mibelli (Knuckle Pad). Presented by Dr. B. K. Das, Dr. D. E. Sevastianos, and Dr. M. M. Jallad.

XIII. Congenital Ichthyosiform Erythroderma. Epidermoid Carcinoma of Right Leg. Presented by Dr. B. K. Das, Dr. D. E. Sevastianos, and Dr. M. M. Jallad.

THE METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

Eliot Wolk, M.D., President
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Murray C. Zimmerman, M.D., Secretary

Jan. 27, 1959

Recurrent Disseminated Afebrile Herpes Simplex in an Atopic Patient Taking Steroids.

Presented by Dr. Murray C. Zimmerman.

This 33-year-old white man has had generalized atopic dermatitis since childhood. He has cleared completely on small suppressive doses of hydrocortisone and other steroid hormones and now takes these only to control a flare. In 1952, he had pustular bacterial infections; in 1954, folliculitis barbae. In 1957, he developed a herpetic lesion on the lip, followed by a disseminated vesicular dermatitis of the face and neck; the Tzanck test was positive for herpes simplex. He had a second episode, almost identical, one year later. He developed his present dermatitis a few days ago, after shaving over a small herpes lesion on the anterior neck.

Most recently the patient has been taking methyl prednisolone, 1 mg. q.i.d. He was started today on triamcinolone, 1 mg. q.i.d., and boric acid compresses to the face. He has no systemic symptoms and feels well.

Physical Examination: diffuse individualized ruptured involuting vesicles scattered over the entire face, anterior neck, and chest; erythema, edema, and crusting. Moderate satellite adenopathy. Patient afebrile.

Discussion

Dr. Harold Price: There is little to be seen at this time other than atopic dermatitis and a superimposed vesicular eruption. I am willing to accept this as recurrent disseminated herpes simplex complicating atopic dermatitis.

The atopic has decreased resistance to viral infection, particularly herpes simplex and vaccinia virus. The atopic infant exposed to herpes simplex virus for the first time may develop a severe frightening explosive dissemination which carries a high mortality. Older children may get repeated attacks, which, however, are usually less severe. This may be as a result of exposure to extrinsic virus or an activation of intrinsic latent virus. I thing it is fairly well accepted that treatment with steroids reduces resistance to infection from various pathogenic micro-organisms, and in this case it is probable that the steroid therapy does have a causal relationship to the repeated herpes simplex infections.

Dr. Rose B. Saperstein: A good rule of thumb is that the presence or absence of open lesions should determine how safe or unsafe it is to vaccinate. I usually vaccinate an atopic in the middle of the back and cover it loosely. If a patient has many open lesions, I should not vaccinate him.

Dr. Fred F. Feldman: Several years ago I studied a number of cases of eczema herpeticum, among them three patients who had recurrent attacks. These cases were reported (A.M.A. Arch. Dermat. 71:399, 1955; *Ann. Allergy* 13:403, 1955). Recurrent eczema herpeticum is probably not as rare as the literature would indicate.

In the past, many cases of eczema vaccinatum were labeled "Kaposi's varicelliform eruption." As suggested by Lynch, this confusion can be eliminated by referring to Kaposi's eruption as "eczema herpeticum" and reserving the term, "eczema vaccinatum" for eczema complicated by vaccinia.

Dr. Zimmerman's patient had pronounced submental lymphadenopathy during the height of his eruption. Marked lymphadenopathy is characteristic of eczema herpeticum. The course of recurrent cases is usually shorter and milder than the primary infection, although not all primary attacks

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are severe. Many cases of eczema herpeticum are unrecognized and considered bacterial infections or even dermatitis venenata. Patients with atopic eczema should be warned against contact with persons who have herpes simplex.

STUART H. MARTEL, M.D.: I don't think there is any doubt that steroids lower resistance to herpes simplex infection. In the last three years, I have treated at least two atopic eczema patients who, while on systemic cortisone, developed repeated bouts of disseminated herpes simplex infection. These patients were not febrile during these episodes but did note an aggravation of pruritus.

DR. CLETE S. DORSEY: I know that theoretically steroids are contraindicated in virus infections. There is experimental evidence to support such a view. However, I have used corticotropin (ACTH) in the treatment of severe aphthous stomatitis accompanied by herpes simplex of the lips, with miraculous results in some instances. The same has been true of some cases of herpes zoster also, in my experience, especially if radiculitis is a prominent symptom.

The reason for this may lie in the fact that the body responds allergically to the virus toxins, and this part of the reaction may respond to the steroids. For example, Stevens-Johnson syndrome, which in some cases, is triggered or caused by the herpes simplex virus, responds dramatically to steroids.

I do not feel that corticotropin should be used if measles or other potentially serious virus infections are present, and probably not often in the treatment of herpes simplex or zoster, but in selected cases of the latter it can be a very helpful medication.

DR. THEODORE B. SUTNICK: An adjunct in differentiating eczema herpeticum from eczema vaccinatum is the Tzanck test. There are intranuclear inclusions in eczema herpeticum and intracytoplasmic inclusions in eczema vaccinatum.

DR. MURRAY C. ZIMMERMAN: Prior to the steroids, I did not see recurrent afebrile herpes simplex in rather mild form, covering a square foot or more of skin. One of the patients that Dr. Martel mentioned said casually on her first visit that she had had six previous attacks of Kaposi's varicelliform eruption. When I expressed skepticism, she proceeded to develop another attack within a short time. Like the patient presented today, she was without fever or systemic illness although about one-third of her body was covered by a widespread herpes infection. She was taking small maintenance doses of steroids.

I am astonished at the extensive discussion of therapy for herpes simplex. There is no more therapy for this than for the common cold. However, it is much easier to prove for herpes simplex, since herpes virus grows in embryonated chick eggs, rabbit corneas, or in rats, guinea pigs, hamsters, mice, etc. Treatments can be tried on these animals and in eggs, and a quantitative response is easily measured. There has been no response to any type of therapy.

If the idea of giving vaccinia vaccine is to stimulate antibody formation, it has long been known that people who get recurrent herpes simplex already have maximum titers of herpes virus-neutralizing antibodies. Only people who never get herpes lack the antibodies. This antibody titer is not increased or changed in any way by vaccinial inoculation or even by intravenous injection of vaccinial virus. It is also not increased by, or subsequent to, any stage of active infection with herpes simplex.

Vaccination, given in the hope of a virus interference phenomenon, is equally irrational. There is no interference phenomenon between vaccinia and herpes simplex virus infections. Infecting a rabbit at any time, with any quantity of vaccinia virus, and in any other fashion injecting herpes simplex virus into it does not modify the course of the herpes infection. The intracytoplasmic Guarnieri body of vaccinia and the intranuclear inclusion body of herpes coexist in the same cell. This suggests that they multiply in association with entirely different constituents of the same cell.

If any of you propose to use γ-globulin as part of your therapy, you can get it through your hospital free, from the Red Cross, if your hospital takes part in the Red Cross blood donation setup. Before using it, it is worth while to get a γ-globulin level. Only if this is below 150 mg. % are the antibacterial antibodies carried by γ-globulin significantly lacking. Patients then have an increased susceptibility to bacterial infection but, strangely enough, usually not to virus disease. Even persons with congenital agammaglobulinemia usually do not have increased virus susceptibility. This has been pointed out as proof that some other immune mechanism is present in virus immunity. If γ-globulin is to be given, an initial dose of 15 to 20 cc., and then a maintenance dose of about 10 cc. once a month, will keep the level up to around 700 mg. %, giving a normal infection immunity to bacterial infections. It will have no influence whatever on most virus infections. Use of γ-globulin in homeopathic doses sometimes recommended in the literature is irrational and futile.

As far as corticotropin or steroids in simplex or zoster, patients may develop these diseases when they are getting either steroids or corticotropin. The number one reason why local hydrocortisone compounds were not released for over-the-counter sale was that herpetic keratitis, normally a relatively self-limited mild infection, is converted by the local use of hydrocortisone into an extremely severe infection, perforating Bowman's membrane, even perforating through the cornea, producing permanent visual damage and even permanent

blindness. This is the number one contraindication for the use of local hydrocortisone.

As far as polio vaccine is concerned in simplex or zoster, I do not see how there could possibly be any effect not attributable to the enthusiasm of the doctor and the suggestibility of the patient. This also goes for post-herpes-zoster serum, moccasin venom, and inactivated herpes simplex virus. This is not to decry any of these forms of therapy, since they are all undoubtedly effective psychotherapeutically. Herpes simplex was treated with psychotherapy by Blank and Brody (*Psychosom. Med.* 12:254, 1950), with as high an incidence of cure as anyone has had. I shall continue to use smallpox inoculation myself in spite of the theoretical objections, because it is easier and faster than a psychiatric interview, or giving the patient a great deal of tender, loving care. I am not at all against the use of placebos for patients —only against placebos for doctors.

Now, as far as using antibiotics are concerned, we all know that there is no antibiotic that will touch simplex or zoster virus. It is unfortunate and humiliating, but we do not have one.

Dr. Feldman gave a much better discussion than I could have of the lymphadenopathy. Sometimes it is hard to differentiate simplex and an early abortive zoster. This lymphadenopathy is to me a very helpful clue. Zoster does not have it, and simplex does.

Porphyria Cutanea Tarda, in Remission. Presented by DR. LAURENCE J. UNDERWOOD and DR. WALTER S. GREEN.

The patient (age 47, Italian descent, olive complexion) was employed until May, 1958, as a core maker (for 20 months), when his hands first erupted. He has been unemployed since then. He noted blisters began appearing where he bumped his hand in his work, and one area "became infected." He continued to have blisters until December. There have been no past illnesses of significance; no similar familial history. "Some" alcohol ingestion is admitted. There is no sun sensitivity. He states the urine has been reddish or dark for many years.

Findings, June, 1958: Small depigmented and violaceous patchy macular and crusted areas on dorsa of hands, with superficial, clean ulcer on right index finger. There were a few clear vesicles. A few crusted areas on the nose and cheek were noted.

January, 1959: No vesicles recently. Purplish suffused patches on dorsa of hands. Depigmented areas at sites of former lesions on hands and face.

Laboratory data, July 22, 1958: Urine, qualitative; porphobilinogen, negative; total porphyrin, strongly positive; total coproporphyrin, positive; uroporphyrin, strongly positive. Paper electrophoretic analysis: "typical for cutaneous type of porphyria."

January, 1959: Urine reveals primary reddish fluorescence with Wood's filter light. Routine urinalysis, blood cell count, and S. T .S.—normal findings.

Discussion

DR. LAURENCE J. UNDERWOOD: The importance of this presentation has been to stress the need for a high index of suspicion to make a prompt diagnosis in porphyria cutanea tarda. (Brunsting, L. A.; Mason, H. L., and Aldrich, R. A.: Adult Form of Chronic Porphyria with Cutaneous Manifestations, *J. A. M. A.* 146:1207-1212 [July 28] 1951). Although it is well known that trauma and sunlight may play a role in precipitating the cutaneous manifestations of this disorder, in an industrial worker with traumatic injuries to the hands the underlying correct diagnosis may be delayed, as happened here.

Bullous Eruption. Presented by DR. JOHN B. WATSON.

Incontinentia Pigmenti with Pruritic Papular Lesions. Presented by DR. STANTON B. MAY.

Case for Diagnosis. Presented by DR. WILLIAM B. REED.

Erythema Annulare Centrifugum? Light Sensitivity Dermatitis? Presented by DR. DONALD ROSMAN.

Case Presented for Diagnosis and Discussion of Management. Hydroadenitis Suppurative in Left Hip Stump. Presented by DR. STANTON B. MAY.

Generalized Guttate Psoriasis. Presented by DR. WILLIAM B. REED.

(Spontaneous) Keloids. Presented by DR. LEONARD E. SAVITT.

Tinea (Tonsurans) of the Scalp in an Adult. Presented by DR. ROSE B. SAPERSTEIN.

Nevus Tardus: Nevus Unius Lateris vs. Epidermodysplasia Verruciformis vs. Lichen Striatus. Presented by DR. HAROLD C. FISHMAN.

Feb. 24, 1959

Adenoma Sebaceum (Pringle Type). Presented by DR. LAURENCE J. UNDERWOOD and DR. WALTER S. GREEN.

This 9-year-old, olive-complexioned boy has had a gradually developing minute, papular eruption on the right cheek since 1954. He is in good health and has had a normal development physically and mentally. He has had no other cutaneous or systemic lesions or defects.

Findings: The lesions are barely elevated, 1 to 2 mm., reddish-brown smooth papules located on

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the right cheek and nose. There are an estimated 15 papular lesions and a few minute pigmented nevi; otherwise his skin is free of defects.

Pathology: The specimen reveals a normal slightly pigmented epidermis, without rete pegs. In the upper and middle cutis, there are numerous dilated capillaries surrounded by round connective tissue cells and melanophores. A few hair follicles are present, but no sebaceous glands. The general appearance of the cutis resembles an angiofibrotic pattern.

Discussion

DR. CLETE S. DORSEY [Slide]: I agree with the diagnosis as presented. Angiofibrotic changes only are present, but "adenoma sebaceum" is a misnomer and describes only one of the many types of skin lesions found in epiloia. This patient has a lesion on the left abdomen just as diagnostic of epiloia as those on the face. This is a small nevus anemicus. This is an uncommon but highly characteristic sign, which, on occasion, is the only cutaneous sign of epiloia. I think Dr. Underwood is to be congratulated on diagnosing this condition when the physical evidence is so minimal. Perhaps later in this boy's life some other part of the syndrome of epiloia will make its appearance. Only by these minimal skin changes would one be able to fit the new symptom into its rightful place in the syndrome.

DR. HAROLD C. FISHMAN: I do not think that there is anything in this slide that even suggests adenoma sebaceum of the Pringle type.

There are three main types of symmetrical, multiple, benign tumors of the central part of the face. One arises from sebaceous glands, of which adenoma sebaceum of the Pringle type is the representative. One arises from the sweat apparatus, like syringomas. One arises from hair follicles, like multiple benign cystic epitheliomas.

There are five different histological varieties of adenoma sebaceum. The Pringle type shows hyperplasia of the sebaceous glands, dilated blood vessels, and increased connective tissue. The Caspary type shows only an increase in the sebaceous glands. The Darier type shows dilated and increased numbers of blood vessels, with no connective tissue or sebaceous gland proliferation. The Hallopeau-Leredde type shows hyperplasia of connective tissue only, with no hyperplasia of the sebaceous glands or blood vessels. The so-called Balzer type, which arises from hair follicles and shows horn cysts in the mid and deep cutis, is a misnomer. It is really multiple benign cystic epithelioma, or epithelioma adenoides cysticum, and not adenoma sebaceum.

The true Pringle type of adenoma sebaceum usually has its onset in early childhood or adolescence. There are small red hard papules, usually on the face. The Pringle type is often associated with the epiloia syndrome, which consists of mental deficiency; epilepsy; tuberous sclerosis of the central nervous system; adenoma sebaceum, usually on the face; subungual fibromas, especially of the toenails, and rhabdomyoma of the kidney and heart or lipoma of the kidney.

Morphea of Scalp. Presented by DR. HAROLD PRICE.

Extensive Leucoderma Secondary to Use of a Bleaching Cream. Presented by DR. JOHN W. CARNEY.

Acroselerosis. Presented by DR. JOHN B. WATSON.

Case for Diagnosis. Presented by DR. CORTLAND MYERS.

METROPOLITAN DERMATOLOGICAL SOCIETY OF NEW YORK

Wilbur B. Hurlbut, M.D., President

Jan. 15, 1959

Mycosis Fungoides. Presented by DR. WILBUR B. HURLBUT.

Pemphigus Vulgaris. Presented by DR. ROYAL M. MONTGOMERY.

Discoid Lupus Erythematosus: Tumor in Nose (For Diagnosis: Lupus Erythematosus Profundus?) Presented by DR. ROYAL M. MONTGOMERY.

Submitted for publication Feb. 25, 1959.

NEW YORK DERMATOLOGICAL SOCIETY

J. Lowry Miller, M.D., President
Frank E. Cormia, M.D., Secretary

Nov. 25, 1958

Dermatitis Herpetiformis of Long Duration, Treated with Diasone. Presented by DR. MAURICE J. COSTELLO.

A group of five patients with dermatitis herpetiformis, showing severe involvement and with a duration of from 6 to 29 years, was shown. All had been treated with Diasone, and excellent control had been achieved.

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Discussion

DR. EUGENE F. TRAUB: This is a very fine demonstration of dermatitis herpetiformis brought

under control. Certainly in the older days it could not have been done. I was amazed at the size of the doses that have been tolerated by these patients. Perhaps the only way you can get a complete remission in these cases is to give a dose to the point of tolerance. It is unique to show five patients who have practically no lesions, especially those who have had the disease for a long time. Diasone certainly seems to be far superior to the other remedies we have used.

DR. GEORGE M. LEWIS: I should like the presenter to discuss the relative toxicity of these drugs and the percentage of poor results in his patients.

DR. G. F. MACHACEK: It is surprising to me that a high dosage has been used in comparison with the relatively low dosage used in a serious disease, such as leprosy. One must take into consideration that quantity changes quality. Do you have a result here that is over and above the usual pharmacological response?

DR. DOUGLAS M. TORRE: Has anyone tried Kynex, which is a sulfonamide with a pyridine radical? It should work as well as sulfapyridine in smaller dosage.

DR. CARL T. NELSON: I can confirm, as can Dr. Chester, of the U. S. Public Health Hospital, the efficacy of Diasone in dermatitis herpetiformis. One can give 3 or 4 tablets over a long period with impunity. Regarding Dr. Torre's question, we treated one patient with dermatitis herpetiformis at Presbyterian Hospital with Kynex, with no benefit.

DR. A. N. DOMONKOS: What is the dose at the beginning, and what does the presenter find to be the maintenance dose?

DR. M. J. COSTELLO: As you know, one of the first drugs in the treatment of dermatitis herpetiformis was sulfapyridine, and it is very effective —probably superior to all others, but it is very toxic. However, since 1937, when I began using it, we have seen only one patient who developed an alarming agranulocytosis, and he recovered. Promacetin is almost as effective as sulfapyridine but less toxic. The young man last presented responded very well to 6 tablets of promacetin and 4 of sulfapyridine, but he is now better controlled with 4 tablets of Diasone a day, alone. I was under the impression for a long time that Diasone was very toxic. Recently, however, we have used it in a fair number of cases, with no toxic manifestations whatever.

As to whether dermatitis herpetiformis is ever cured, the first patient I ever treated had had the disease for eight years and was completely cured after three weeks of treatment with sulfapyridine. Usually, there are very few remissions and many exacerbations.

The effective dose of Diasone varies. Some patients will require 6 tablets a day, others 3 consistently, and others 1 every day or every other day. It seems to us that the severer and more extensive the eruption, the greater the dose must be, though that is not always so. There is a tremendous specificity in the dosage. Sometimes 3 tablets will control the eruption where 2 will not.

The only objection to the use of Diasone is the blue color of the skin, caused by methemoglobinemia. We have not used Kynex, which is known to be associated with severe purpura.

We give these patients 3 gm. of Diasone a day, 4 gm. of Promacetin, and 6 tablets of sulfapyridine and the maintenance dosage is determined from that.

Generalized Discoid Lupus Erythematosus.

Presented by DR. MAURICE J. COSTELLO.

A Chinese boy aged 3 years was first seen on July 29, 1957, with an eruption on the face, elbows, knees (extensor surfaces), knuckles, and ankles, which had been present for two years. There was generalized muscular weakness, poor appetite, failure to gain weight, and pain in the muscles and joints, especially the knees and ankles. Roentgenograms of the ankles and knees showed questionable soft-tissue swelling of the left knee. He was taking small doses of prednisone (Meticorten) for the arthritic type of pain.

Examination showed pinkish, slightly atrophic, slightly scaly, sharply defined plaques over the knuckles, and slightly pink, atrophic scarring on the elbows, knees, and ankles. The face showed dusky erythema ("heliotrope" color).

A diagnosis of probable lupus erythematosus was made, and the child was hospitalized for 10 days. Small, subcutaneous abscesses developed on both arms, and culture showed Staphylococcus pyogenes var. aureus. He was treated with penicillin and erythromycin (Ilotycin). A biopsy specimen of a lesion on the right elbow showed active chronic dermatitis. Muscle biopsy specimen was normal. Four L. E. preparations were normal; serologic tests for syphilis were negative, and blood cell counts and urinalyses were normal. The ASO titer was less than 12 Todd units; blood urea nitrogen was 12 mg., and creatinine was 0.9 mg. Sheep-cell agglutination was negative.

On April 7, 1958, the patient was given triamcinolone (Aristocort). He developed mild paronychia which was treated with erythromycin. Since then, the child has improved slowly. He has normal muscular strength; his appetite is fair, and he is active and playful. His facial color is almost normal, and the lesions on the knuckles are less scaly and less erythemic.

By Sept. 22 the boy had developed some hirsutism on the face while receiving Aristocort twice a day. The dose was reduced and the hirsutism had decreased in one month.

Discussion

DR. GEORGE M. LEWIS: I am sure Dr. Costello must have had dermatomyositis in mind, and I should like to ask how he ruled that out. While we are seeing the patient with residua and not much activity, the evidence tonight would seem to favor the combined disease. It is unusual to see lesions of discoid lupus erythematosus responding to steriod therapy, which would seem more appropriate for dermatomyositis.

DR. A. C. CIPOLLARO: A biopsy specimen of the muscle was normal.

DR. WILBERT SACHS: I also could not correlate the muscle lesions with discoid lupus erythematosus. It is surprising that the child had so much difficulty with the muscles, and still findings on biopsy of the muscle were normal.

DR. DOUGLAS M. TORRE: I agree with Dr. Lewis that clinically it looked more like dermatomyositis. With a diagnosis of lupus erythematosus, I am wondering why antimalarial drugs were not used before triamcinolone was tried.

DR. L. P. BARKER: The erythema and edema of the eyelids, the muscle weakness, and prompt response to treatment with steroids are all in favor of a diagnosis of dermatomyositis.

DR. CARL T. NELSON: I thought this was dermatomyositis from the history, and, as Dr. Barker says, one has great difficulty in getting past that diagnosis. We expect 50% of children with dermatomyositis to undergo spontaneous resolution.

DR. FRANK E. CORMIA: I think, too, that another factor to be considered in children and even in adults is that the skin lesions in dermatomyositis may markedly resemble those of lupus erythematosus.

DR. EUGENE F. TRAUB: I, too, agree with those who feel that it is more likely an example of the syndrome of dermatomyositis. However, it could be just a type of lupus erythematosus in a patient with malnutrition. Sometimes we get rather a degree of malnutrition in the Chinese. I should not like to call it discoid lupus erythematosus, even if we put it in the lupus erythematosus category. I think it is definitely a disseminated, subacute process.

DR. WILBERT SACHS: I do not recall having seen atrophy in lesions, as in this child. They are usually more like scleroderma.

DR. J. LOWRY MILLER: I should agree with a diagnosis of dermatomyositis.

DR. M. J. COSTELLO: There are three things one should find in dermatomyositis which are not present in this case. The muscle biopsy was normal, the creatinine was negative, and the eruption as we saw it in the beginning was not characteristic. I do not think this is dermatomyositis. In the beginning I think the child had acute or subacute lupus erythematosus. He has had a fever every since the eruption began and had arthritis, which I think accounted for some of his difficulty in getting off the floor. He never did have any difficulty with his grip. I put it in the group of discoid lupus erythematosus because we never found the L. E. cell, but the erythrocyte sedimentation rate was always rapid. I think the cutaneous lesions are those seen in lupus erythematosus and not those of dermatomyositis, which are more evanescent.

Paget's Disease of the Vulva. Presented by DR. ANTHONY N. DOMONKOS.

A white, 68-year-old spinster, has had rheumatoid arthritis for many years. In 1956, an operation was performed on the hip for an abscess. Shortly before the operation she had pruritus of the vulva, and she was first seen in January, 1958, for this complaint. Fungous examinations at that time and on several subsequent occasions were negative. In July, 1958, the patient was seen again with a herpetic type of eruption on the right labium majus. A steroid hormone ointment gave relief from itching for several months. On Nov. 6, a biopsy was performed.

On the right labium majus is an erythematous, slightly infiltrated, swollen area approximately 5 cm. in diameter. No lymph nodes are palpable in the inguinal region.

The biopsy, reported by Dr. Gerald F. Machacek, showed a somewhat thickened epidermis with a large area of swollen, pale cells having a reticulated cytoplasm and nuclei of various sizes, some pale and others deeply staining. There was evidence of hyperkeratosis and a slight parakeratosis. The granular layer over the area of abnormal cellular proliferation was for the most part indistinct or very thin. Similar cells were seen proliferating from the walls of a hair follicle. The underlying cutis showed evidence of chronic inflammatory reaction. Sections stained for mucin disclosed this substance in the large, abnormal cells. This would indicate that the cells are not those of a melanoma but of Paget's disease. Diagnosis: Paget's disease of the skin of the labium majus.

Discussion

DR. DOUGLAS M. TORRE: The usual concept of Paget's disease is of an intraductal tumor extending out to the skin. There are no ducts here, certainly of the mammary type. Whether Skene's glands or the apocrine glands can act that way, I do not know.

DR. L. P. BARKER: Clinically, I think this patient has Bowen's disease, and I should treat it as such.

DR. CARL T. NELSON: This seems to be an intraepidermal epithelioma. Clinically, I should

agree with Dr. Barker that Bowen's disease should be considered.

DR. ORLANDO CANIZARES: I agree with Dr. Nelson.

DR. FRANK E. CORMIA: It certainly had a demonstrable border as well as a rather diffuse process, such as one sees in Paget's disease of the breast. I am not so sure it is not Paget's.

DR. M. J. COSTELLO: I think it is Bowen's disease.

DR. EUGENE F. TRAUB: We presented a number of cases with Dr. Casper. Everybody who saw the sections agreed it was Paget's disease, but when we mentioned the locale it immediately caused a discussion. I think it is now generally accepted that extramammary Paget's disease can occur, and this might conceivably be an early case. I should even doubt somewhat that this case is malignant, but if it is I should rather believe it was a very early case of Bowen's disease than of Paget's disease.

DR. J. LOWRY MILLER: On inspection alone, I should diagnose Bowen's disease, but Paget's disease in the early stages may look like this.

DR. A. C. CIPOLLARO: The older pathologists did recognize extramammary Paget's disease. I do not know whether modern pathologists hold to that opinion. Clinically, it is impossible at times to differentiate Paget's disease from Bowen's. Both may ulcerate, both may produce tumors, and both may give an eczematous or psoriasiform picture. Invariably, a thread-line border is observed in both of these diseases. This patient's lesion shows such a border. The prognosis in Paget's disease is not as serious as when it attacks the breast. Patients with extramammary Paget's disease have gone on for years without involvement of the glands or remote metastases.

DR. WILBERT SACHS: I am well aware that cases of extramammary Paget's disease have been described in the literature, but if I may be permitted to have an opinion, no matter how wrong, I do not believe in extramammary Paget's disease and believe this is Bowen's disease.

DR. GEORGE C. ANDREWS: I believe that extramammary Paget's disease arising from an apocrine gland is a well established entity, and I believe that is accepted by the best pathologists.

DR. A. N. DOMONKOS: I read the case presented by Dr. Traub in 1943 before this society. All agreed with the diagnosis of Paget's disease histologically. That patient died some five years later with carcinomatosis. Paget's of the vulva clinically may resemble Bowen's disease, and histologically it may also. In 1954, Lennox and Pearse were able to show a mucin reaction in all of four cases of Paget's disease of the vulva, signifying that it is not of epidermal origin but from the glandular duct epithelial cells (*J. Obst. & Gynaec. Brit Emp.* 61:758-761 [Dec.] 1954). They said the mucin reaction was not found in Paget's disease of the breast.

In all, there have been about 60 cases reported of extramammary Paget's disease—about 18 in the male. It was originally thought of as a precancerosis, but is not considered an intraductal carcinoma originating in the apocrine glands.

In regard to therapy, the other case, which was not presented tonight but whose slides were shown, had an extensive removal of the lesion by simple excision and closure. That was done exactly a year ago and the patient is well and has shown no evidence of recurrence. I believe here again vulvectomy on the right side should be the therapy.

DR. WILBERT SACHS: There is a difference in therapy. If you feel it is some type of Paget's disease, the therapy must be much more heroic than if it is Bowen's disease.

DR. FRANK E. CORMIA: Bowen's disease of the mucous membranes is more malignant than that involving the skin.

DR. GEORGE C. ANDREWS: Yes, when the mucous membranes are involved it is more malignant than on the skin.

A Case for Diagnosis (Dermatitis Factitia, Pyoderma?) Presented by DR. EUGENE F. TRAUB.

Chronic Onychia and Paronychia. Presented by DR. DOUGLAS TORRE.

Prickle-Cell Epithelioma. Presented by DR. MAURICE J. COSTELLO.

Folliculitis Decalvans. Presented by DR. MAURICE J. COSTELLO.

Epithelioma. Presented by DR. MAURICE J. COSTELLO.

Erythema Multiforme (Drugs). Presented by DR. FRANK E. CORMIA.

Discoid Lupus Erythematosus Occurring Simultaneously in Two Sisters. Presented by DR. MAURICE J. COSTELLO.

Jan. 27, 1959

Discoid Lupus; Reticulated Livedo of Legs, Cryoglobulinemia. Presented by DR. CARL T. NELSON.

The patient is a white woman, aged 44 years, from Presbyterian Hospital.

History: This patient was first seen one year ago because of pruritic, reticulated, erythematous, and vesicular plaques on the lower legs and ankles of 18 months' duration. Her past history is significant in that she has had discoid lupus of the ear lobes and face for 12 years (confirmed by biopsy). Seven years ago, she developed jaundice following a series of gold injections. She has had two normal pregnancies and six miscarriages. Approximately three years ago, the patient developed arthralgias and intolerance to cold and found she tired easily. The reticulated livedo of the extremities and the pruritic, erythematous, and vesicular plaques of the lower legs became prominent and have persisted off and on since then.

Examination shows an asthenic woman with livedo reticularis of the extremities, with erythematous papules and plaques on the lower legs and ankles. These are pruritic, and in some areas crusting and vesiculation are evident. Dormant lesions of discoid lupus are present on the ears. The face is clear. Physical examination is otherwise within normal limits. There are no dermatologic lesions suggestive of systemic lupus.

Laboratory: Urinalysis, albumin 1+; ESR 30 mm.; Hb. 13.8 gm.; WBC 8,650 (normal differential); VDRL 1+, TPI negative; LE preparation negative. Liver-function tests, ECG, and BUN normal. Cryoglobulins positive. Chest x-ray normal. Serum albumin 4.4 gm.; globulin 2.7 gm.

Biopsy: None recently.

Course and Treatment: The lupus erythematosus has been controlled with chloroquine, 250 to 500 mg. daily. The cryoglobulinemia has been present and absent at various times during the past year. The erythematous plaques on the lower legs have improved since Decadron, 1.0 mg. daily, has been given, but the livedo remains unchanged. Except for the suggestive laboratory findings and the arthralgias, there has been no clear-cut evidence of systemic lupus.

DR. MACHACEK: Some of these cases are diagnosed as livedo reticularis with summer ulceration; yet, these will occur with the ulceration in the winter as well as in the summer.

DR. LEWIS: Perhaps, Dr. Nelson would discuss the vagaries of cryoglobulinema when he closes. I wonder whether pernio should not be considered in connection with what Dr. Miller has mentioned —lupus diathesis. The diagnosis of pernio is not made very often in this country, and, yet, it might be apropos here.

DR. BARKER: The joint pains, malaise, and increase in sedimentation rate are indicative that discoid lupus erythematosus is progressing into the subacute or acute disseminated state. When patients with discoid lupus get overtired, run down, or poorly nourished, they are more prone to develop the acute phase of the disease.

It is interesting that some patients with livedo reticularis also have cryoglobulinemia. The significance of this finding is not known, but it could possibly explain why some of these patients develop ulcerations during cold weather.

DR. NELSON: This patient has smoldering lupus, as evidenced by her current laboratory findings, and it may very well be that she will systematize. She has been admitted to the hospital on two occasions, just because I thought she had probably arrived at that stage.

Regarding Dr. Lewis's question, cryoglobulins, when they are present in relatively small amounts, may be found on some occasions and may be missed on others. This woman has only a small amount of cryoglobulin in the blood.

Cryoglobulins are cold-precipitable fractions which vary in their molecular weights from 160,000 to well over 1,000,000. They are found particularly in cases of lymphoblastoma, multiple myeloma, leukemia, kala-azar, so-called Raynaud's syndrome, and infections like subacute bacterial endocarditis. Up to now, it has been thought that cryoglobulins occurred in lupus erythematosus only rarely. However, at Presbyterian Hospital, we have found them not infrequently associated with lupus of the smoldering type.

The dermatologic manifestations that should prompt one to look for these cold-precipitable globulins are livedo, Raynaud's symptoms, acrocyanosis, cold intolerance, unexplained purpuras, and urticarias, and ulcerations of the digits or the lower extremities.

There are other manifestations that accompany cryoglobulinemia, when the cold-precipitable fractions are present in large amounts. Arthralgia is one of them. Some of these people also develop deafness, vascular occlusions, sludging of blood in conjunctival vessels, retinal hemorrhages, and bleeding from the gums. For these signs to develop as a result of or as an accompaniment of cryoglobulinemia, however, relatively large amounts of cold-precipitable globulin usually must be present.

DR. TRAUB: Have they examined a large series of normal persons to find out if cryoglobulins can be found in normals?

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DR. NELSON: Yes; as a matter of fact, they have. Normals apparently do not have this condition.

DR. MILLER: Bearing on this question, we did a series of 120 patients who were STS-positive cases, diagnosed as biological false-positive reactors. A number of laboratory tests, including cryoglobulins, were done. All were completely negative, except one case which had already been classified as a cryoglobulinemia.

DR. COSTELLO: Does it occur in all the collagen diseases, like scleroderma, dermatomyositis, polyarteritis nodosa?

DR. NELSON: It occurs in polyarteritis nodosa and scleroderma. I do not recall any cases of dermatomyositis with cryoglobulinemia.

Pemphigus Vulgaris. Presented by DR. ANTHONY N. DOMONKOS.

History: A 49-year-old housewife has had a bullous eruption for one year. She had had good health until her present illness. Approximately six weeks after the generalized bullous eruption on her body, large painful erosions appeared in the mouth. Seven months ago, eight severely abscessed teeth were removed. Since that time, her mouth has been practically free from lesions. During the past year, she has had recurrent moniliasis under the breasts and on the axillae, vulva, and vagina. Within the past six months, there has been a weight gain of 32 lb., her present weight being 218 lb. Intermittent glycosuria started eight months ago. Constant glycosuria has been present for two months. Throughout her illness, she has been completely ambulatory and able to perform most of her household duties.

Description: At present, the patient has scattered erythematous, slightly foliaceous lesions on the scalp, sides of the face, chest, back, and inguinal regions. Several bullae on the body have been noted for the past several weeks. Hirsutism, buffalo hump, and moon face are present.

Laboratory: Urinalysis: albumin negative; glucose, 4+; sedimentation rate 8 mm. in 60 minutes on April, 1958, 15 mm. in 60 minutes on Jan., 1959. Blood studies: for past eight months, hemoglobin 13.5 gm. %; WBC, eight months ago, 32,000 with 58% polymorphonuclear cells, 39% lymphocytes, and 1% eosinophils; at present, 20,000 with 52% polymorphonuclear cells, 47% lymphocytes, and 1% monocytes; blood glucose at present, 244 mg. %. BP has been around 120/80 during the past eight months.

A biopsy performed at the beginning of the illness showed a ruptured intraepidermal bulla with acantholytic epidermal cells.

Course: At the onset, trial medication with sulfapyridine produced no improvement. In April, 1958, prednisone, 70 mg. daily, was prescribed, and the patient was kept at this dose for six weeks, then 60 mg. for the next four weeks, and then gradually reduced to 25 mg. daily in Aug., 1958. At that time, medication was changed to Dexamethosane and continued to the present, the daily dosage varying from 1.35 to 2.25 mg. Weekly injections of corticotropin (ACTH) 40 mg., have been given. For the past three months, chlorpropamide, 500 mg., has been taken daily.

DR. MACHACEK: Usually, cutaneous lesions disappear, but mouth lesions, even on large dosage, will remain. In this rather complicated case, the mouth lesions are relatively minor, having improved, and the erythematous lesions of the Senear-Usher type have remained.

I agree that the potassium level should be ascertained, because of the use of the steroid and the diabetes. Insulin should be used. Speaking of oral antidiabetic agents, I think that chlorpromide (Diabinese) is probably more hazardous than tolbutamide (Orinase). There have been several reactions to it which I myself have seen. In any case, I do not think this patient is a candidate for oral antidiabetic therapy.

DR. LEWIS: In the early days of treatment of pemphigus with corticotropin and corticosteroids, the tendency was to give very large doses. I know of several patients who died, not from the disease but from overenthusiastic use of this type of therapy. I have felt for some time that conservative therapy is indicated, having as its aim not the obliteration of every blister or to get rid of every sign of the disease, but, rather, to keep the patient working and useful and moderately healthy.

I thought, when this patient was presented tonight, that Dr. Domonkos should be congratulated on the skillful way he has handled a difficult problem. I should agree with him that bigger doses are not warranted as long as the patient is in as good shape as tonight. There should not be too much real difficulty now in handling this patient. The disease is chronic and difficult to eradicate, but I do not think this patient is going to "go bad."

DR. COSTELLO: I have not got it clear in my mind as to whether this patient had a more extensive eruption than she presents as the present time, but I would be inclined to think that she has Senear-Usher type of pemphigus because of the distribution of the lesions on light-exposed areas. The bullae are mostly above the waist. The question comes up here as to whether the treatment is adequate, whether it would have been better to give this patient larger doses in the beginning and taper off, whether it was wise to give her conservative therapy. I do not think, in my experience, this type of pemphigus is the

most refractory to treatment. It requires large doses of the steroids, and, even with big doses, they do not do well. I have a number of patients with pemphigus vulgaris who have cleared under conservative treatment, on 12 tablets a day of any of the steroids chosen for the first few weeks. They were then maintained and some cured on 4 tablets a day. Some required no further therapy. However, I have had other patients, such as the one presented, where they have had an eruption on the areas, but they were not budged by treatment at all, and, if they were improved, it was only by large doses over long periods of time. I repeat, in my experience, the Senear-Usher type is the most refractory to therapy.

If I were to treat this patient, I would treat her by giving her corticotropin, 25 to 50 units in intravenous infusion over an eight-hour period for 10 days. I think, as the initial form of therapy, that is very worth while in pemphigus erythematosus and in severe pemphigus.

DR. NELSON: I agree with Dr. Costello regarding the difficulty in treating certain cases of the Senear-Usher type of pemphigus vulgaris. Some respond to relatively small dosages of corticosteroids, and yet some of the most difficult types of pemphigus to treat are these cases of Senear-Usher disease. I do not know how far Dr. Domonkos wants us to go into the management of this case, but I have several comments on the treatment given thus far.

First of all, I do not think the patient is receiving enough steroid at the moment. She is getting 1.5 mg. of Decadron, which is the equivalent of about 45 mg. of cortisone. I doubt very much that this will have any therapeutic effect in this type of patient. If the dosage of steroid is elevated significantly, potassium should be given as a supplement. This patient is receiving Diuril, which is a known cause of loss of potassium.

Diabetes may occur in people receiving large doses of Decadron. It is diabetogenic, but perhaps not as much so as methylprednisolone (Medrol). We have induced diabetes in patients on relatively large doses of Decadron. In this case, however, the patient probably was prediabetic or diabetic before therapy was started, as I gather from the history. If she was diabetic before treatment was started or is now diabetic at the age of 49 years, I do not believe that one should attempt to control the condition by the use of chlorpropamide or Diabinese. These compounds may be suitable for oldsters with diabetes but not for patients at this age.

DR. CORMIA: I had somewhat the same thoughts that Dr. Nelson did, and, certainly, with regard to the Diuril, which is a cause of marked potassium depletion when given over a period of time. If one gives it intermittently for short courses, it does not seem to affect electrolyte balance very much, but, if given over a long period of time, this possibility should be checked, particularly since this patient is receiving steroids. I think, if there is any other way to manage the patient without the Diuril, it would be definitely worth while. On the other hand, I do not know that I am completely in contradiction to what Dr. Domonkos said about the use of adjuvant drugs to control the diabetes. After all, what are you going to do in the presence of mild steroid-induced diabetes? What would you suggest as a replacement?

DR. NELSON: Insulin.

DR. DOMONKOS: Thank you for this very thorough discussion. In answer to Dr. Costello, I had a difficult time when I wrote up this report as to whether I should call this pemphigus vulgaris or Senear-Usher at the present time. I believe she had pemphigus vulgaris at the time I first saw her.

Secondly, on 60 mg. of prednisolone I was able to control her lesions completely. She was free of lesions. However, the interesting feature of this patient, which, I am happy to see, Dr. Lewis appreciated, was the fact that this is a woman, who is active, who goes about her household duties; in fact, she even works in her husband's shop. I felt, with the situation as it is, that if I could keep her relatively symptom-free, it would be much better than trying to give her huge doses of steroid therapy and getting this completely suppressed. Even on small doses, she has developed many of the symptoms of steroid therapy. She has diabetes, she has the "buffalo" neck, the tremendous gain in weight, and, perhaps, some other symptoms.

I appreciate very much the comments on the potassium balance. I think that should be investigated, which has not been done.

The only other comment I would like to make is with regard to the chlorpropamide. There has been only an intermittent glycosuria up until about four weeks ago. With that in mind, I felt that it would be better to try to control this situation with oral medication. It is apparent that it does not control her diabetes.

Leukoblastic Infiltration of Skin: Probably Monocytic Leukemia. Presented by DR. GERALD F. MACHACEK.

Patient: Negro, aged 58 years.

Complaint: Eruption on chest and back; duration, between six and eight months.

History: In January, 1955, patient had an enlargement of his thyroid which was resected because of respiratory difficulty. He also suffered from hypertension; a positive serology. I^{131} uptake was 31%; BMR, —18. He was considered to have Hashimoto's disease and ultimate diagnosis of

thyroiditis, Type ?, was made. A 1 cm. lymph node was removed at this time, but there is no record of its description. His BMR, April 16, 1956, was —51. PBI, Jan. 6, 1958, was 8. He is maintained on thyroid 0.3 o. d.

About eight months ago, patient developed a rash on his back and chest.

Description: Over the interscapular area, there is a symmetrical zone of hyperpigmentation with focal collections of lichenoid papules which are indurated. Diascopic examination revealed these papules to be slightly yellowish and discrete, though tightly grouped. Over the chest are less distinct round and oval areas of hyperpigmentation which feel somewhat infiltrated. The patient complains of some pruritis. The liver is 2 finger-breadths beneath the costal margin. The heart is enlarged, and there is a systolic and diastolic murmur.

Laboratory examinations: The serologic test for syphilis is positive. X-ray of chest shows cardiomegaly and congestion of the right lower lobe of the lung. The ECG reveals a left axis deviation. ESR, 13 mm. per hour. Blood studies: 11.8 gm. hemoglobin; RBC 4,190,000; WBC 4,550, with platelets normal, polymorphonuclear cells 19%; lymphocytes 46%, and monocytes 35%.

Biopsy revealed an infiltration of large mononuclear cells, which, for purposes of classification, was called a lymphosarcoma, but leukemia was suspected.

Discussion

DR. NELSON: I do not want to compliment my own staff, but this seems to me to be a fairly astute clinical diagnosis. The intriguing point is whether this man had leukoblastic infiltration of the thyroid at the time of his operation for so-called Hashimoto struma. If so, this would be a most unusual situation. Dr. Nataro, in passing, tells me that this man received 5 grains of thyroid a day. He wonders if this will supply sufficient iodine to raise the possibility of an iodide eruption in this case.

DR. SACHS: It was my impression that monocytic leukemia, under the microscope, is a fairly easy diagnosis to make, and, with the description by Dr. Machacek, I should certainly have to agree with that diagnosis. The only point that I should like to raise, in those cases that I have seen, is that I have never seen a patient with the same type of cells not present in the blood and the WBC raised much higher than 4,500.

DR. MACHACEK: Well, we have leukemias with 10,500.

DR. SACHS: But not monocytic leukemia. I have not seen it.

DR. MACHACEK: I have tried to tie this cutaneous condition to the original thyroiditis. We considered Hashimoto's disease and thyroiditis of unknown type. Other pathologists who have examined sections of skin from this patient do not accept the diagnosis of lymphosarcoma or leukemia. They classify the case as one of mycosis fungoides.

It should not be forgotten that the patient also has syphilis.

However, in looking somewhat superficially into the problem, I did discover that in several hundreds of cases of lymphomatous thyroid, it was found that the thyroid was apt to be involved in an ultimate neoplastic affection, including lymphosarcoma, rather than thyroid cases without a lymphomatous thyroiditis. We have here a neat problem and one, I think, worth showing.

Diagnosis: Vasculitis? Panniculitis? Presented by DR. FRANK E. CORMIA.

Case for Diagnosis: Pyoderma Gangrenosum: Sickle-Cell Anemia. Presented by DR. MAURICE J. COSTELLO.

Onychia and Paronychia Due to Staphylococcus Aureus. Presented by DR. DOUGLAS TORRE.

Feb. 24, 1959

Xeroderma Pigmentosum. Presented by DR. ANTHONY N. DOMONKOS.

History: A 10-year-old girl of Italian extraction first developed excessive pigmentation on the sun-exposed areas, such as face, chest, arms, and legs, at the age of 5 years. Prior to development of lesions, it was noticed that the child had photophobia. Since that time, the sun-exposed areas have become progressively darker with increased freckling of the skin. Prior to this time, a lesion on the left ala nasi had been removed in Argentina. The lesions seen today on the face have developed within the past year. The mother of the child is a niece of the father. This is the father's second marriage.

Description: On the face, neck, arms, and legs there is an increased pigmentation upon which are superimposed numerous freckle-like macules. Some telangiectasia and atrophic spots are present. At the right outer canthus there is an epithelioma 5 mm. in diameter, and at the right upper lip there is another epithelioma, 1 cm. in diameter. There is a cutaneous horn near the right nostril, 3 mm. in diameter, and at the angle of the mouth on the

right side there are three small similar lesions. She also has an epithelioma on the right chin.

Blood studies: Hgb. 13.2 gm., 87%; RBC 4,577,000; leukocytes 11,100, with polymorphonuclear cells 70%, lymphocytes 20%, monocytes 2%, eosinophils 8%.

Urine: negative for porphyrin.

DR. TORRE: At the American Academy of Dermatology meeting in December, someone brought up the idea of possibly abrading these patients. I was wondering whether anyone had seen any cases that had undergone abrasion and whether the result was satisfactory. Dr. Traub's patient developed melanoma in both eyes. I was not aware that melanoma was likely to be caused by light sensitivity. These patients must be protected indoors as well as out.

DR. COSTELLO: I did not see this patient, but I am wondering if she has been given Oxsoralen at all. She probably does not expose herself to light.

DR. TRAUB: This is an interesting case because of the age of the patient. The outlook for this patient is not at all good. She will keep getting lesions, and finally she will get to the point where she will be so pathetic that death would be preferable.

These patients get lesions more on the face, but, nevertheless, even on the covered areas of the body, where sun can be completely avoided, the disease is progressive. Protection, however, from sunlight is of some help. Yet, the disease is relentlessly progressive.

DR. LEWIS: Have antimalarial drugs been prescribed?

DR. CIPOLLARO: There are two points I should like to bring up. First, the literature indicates that melanoma, basal- and squamous-cell epitheliomas, and sarcomas develop in patients with xeroderma pigmentosum. I bring this up because many have the erroneous conception that only squamous-cell epithelioma develops in xeroderma pigmentosum. The other point I wish to emphasize is that surgical planing for the treatment of xeroderma pigmentosum may be very dangerous and I certainly do not favor it.

DR. ANDREWS: I think Dr. Domonkos brought up the consanguinity of the parents.

In addition to the tumors that Dr. Cipollaro mentioned, there are also benign tumors, angiomas, and fibromas. In reference to the cases that develop late in life, they are the atypical cases, the forme fruste type. They are never severe, like this child. They usually consist of excessive freckling on exposed parts and may tend to form a few tumors, but they are formes fruste of the disease.

DR. TORRE: I was wondering whether any studies had been done to see whether other ranges of light affect the skin as well as ultraviolet, such as visible and fluorescent.

DR. ANDREWS: It has been studied; the sensitization of such patients to various wave lengths, and also sensitivity of x-rays of different wave lengths.

DR. CIPOLLARO: They are supposed to be sensitive to all light, even ordinary light. That is what the literature indicates. They are also sensitive to heat.

DR. DOMONKOS: In answer to Dr. Sachs' question about xeroderma pigmentosum arising recently in this child, it has been stated in the literature that it may arise as late as 25 years of age or 30 years of age. Of course, these are very unusual. Usually, they arise shortly after birth.

The question arose as to the advisability of planing these lesions, about which Dr. Cipollaro has already commented. There is one other case of which I know—a young boy who actually did have planing done. They gave antimalarials; the child has had the benefit of planing, Oxsoralen, and antimalarials, and none of these, alone or in combination, has retarded the development of new lesions.

Dermatitis Herpetiformis? Presented by DR. CARL T. NELSON.

The patient was a white boy, aged 3 years.

The complaint was generalized vesicular and bullous eruption of three months' duration.

History: The patient was entirely well until Nov. 20, 1958, when he developed vesicles and bullae on the legs and buttocks. These lesions arose from erythematous bases and ultimately became generalized. No mouth lesions were noted, and none has developed since then. The patient was hospitalized and treated with corticosteroids (from 40 to 100 mg. of cortisone equivalents daily), antibiotics, nicotinic acid, immune globulin, and sulfapyridine. Response to these medications was doubtful, and the patient continued to develop new lesions.

The patient became febrile and consistently showed a leukocytosis (25,000 to 39,000 WBC with 8% to 10% eosinophils). Finally, a clinical remission occurred when the patient was given 25 to 40 units of corticotropin (ACTH), 1 gm. of SAP, and 100 mg. of nicotinic acid daily. However, attempts to lower the dosage of these medications resulted in exacerbations of the dermatitis.

Examination: Except for the dermatitis, the general physical examination is within normal limits. Some Cushingoid changes have occurred, and the liver is palpable 4 cm. below the right costal margin.

Laboratory: RBC 4,400,000; WBC 39,000 (polymorphonuclear cells 49%, lymphocytes 34%, monocytes 9%, and eosinophils 8%), to 11,300 (polymorphonuclear cells 27%, lymphocytes 69%,

monocytes 0%, and eosinophils 4%); platelets adequate; urinalysis, bone marrow biopsy, stool examination, STS, chest x-rays, normal.

Biopsy of skin: Interpreted as compatible with dermatitis herpetiformis.

Course: The patient was discharged from the hospital on Jan. 9, 1959. Aristocort (6 to 8 mg. daily) was substituted for corticotropin and Diasone, 0.3 gm. daily was given instead of SAP. On this regimen, the patient has continued to develop new skin lesions, but he remains febrile and in good spirits.

Discussion

DR. LEWIS: There is some superficial resemblance to fungus infection. While some lesions have disappeared spontaneously, that is not entirely unknown with superficial inflammatory fungus disease. I was also interested in the questioning that went on with regard to drugs and believe it possible that this erythema multiforme-like eruption might be caused by a drug such as iodide.

DR. CORMIA: I think that Dr. Lewis's suggestion is a good one. The patient may possibly have an atypical drug eruption. Penicillin, for example, can produce a bullous eruption that looks a little like this. Penicillin in milk may have produced it, and this possibility should be investigated. Finally, in occasional patients with dermatitis herpetiformis, one may achieve a spectacular result by removing any focus of infection. If this child has large and presumably infected tonsils, that might be another avenue of approach.

DR. BARKER: I do not think drugs have been ruled out. Iodized salt was discontinued only yesterday, and vitamins with minerals contain iodine.

The palpable liver and spleen in infants are of no significance; also, children normally have lymphocytosis.

I agree that bullous eruptions in infants are often very difficult to classify. A child with a bullous eruption was presented by me before this society and a diagnosis of dermatitis herpetiformis was suggested. The child was given Promacetin, Diasone, and, finally, large doses of steroid, without any beneficial effects on the eruption.

DR. COSTELLO: I believe that if an adult has dermatitis herpetiformis, the eruption will clear completely in the matter of a week on sulfapyridine, Promacetin, or Diasone therapy. This has been my invariable experience in treating dermatitis herpetiformis. However, in vesicular and bullous eruptions which simulate but are not dermatitis herpetiformis, in children, this does not happen. I am inclined to think that certain vesicular eruptions which occur in children are not dermatitis herpetiformis but an eruption that I cannot label accurately.

This child has had sulfonamide treatment. The eruption should have cleared if it were dermatitis herpetiformis. Dr. Cipollaro has had two cases of the polymorphic pustular type of dermatitis herpetiformis which responded very well to the sulfonamides. I have a patient now of Dr. Cipollaro who is controlled completely by taking one tablet of Diasone a day.

DR. TORRE: I should like to ask Dr. Costello, referring to his statement about dermatitis herpetiformis in adults, if it does not clear after one week, it is not dermatitis herpetiformis, what dosage of Diasone does he give?

DR. COSTELLO: One tablet, three times a day. If the eruption does not clear up under adequate therapy in a reasonable time, I do not believe that the eruption is dermatitis herpetiformis, especially if Diasone is used.

DR. TORRE: Is it 300 mg?

DR. COSTELLO: It is 0.33 gm.; 330 mg. May I ask, is there anything in this eruption to suggest Hailey-Hailey?

DR. SACHS: No.

DR. MILLER: I think that the possibility of inflammatory creeping eruption should be looked into very thoroughly. I had two cases from down in that section last summer, and one of them was very inflammatory and resembled to a certain extent the lesions that are present here.

DR. DOMONKOS: I should agree with Dr. Cipollaro when he called our attention to the blood cell count, and the fact that when a child is given steroid therapy, certainly in many cases of lymphoblastomas or leukemias, it will tend to bring down the blood cell count. I suggest that the child be taken off steroid therapy to see what happens to the blood picture, because this could be dermatitis herpetiformis due to a lymphoblastoma of some sort.

DR. CANIZARES: This presents problems of diagnosis. There has been some improvement with Diasone, which would apparently seem to put it more into the group of dermatitis herpetiformis. Possibly, Dr. Costello is right in separating this form as a different variety, but I think, most likely, we will have to accept it as a more resistant type, clinically somewhat different, especially in children, but still dermatitis herpetiformis. After all, you can make a different entity. Otherwise, we have to fall back into entities we already know, but into which the patient does not fit entirely.

DR. ANDREWS: I feel, as the two preceding speakers do, that this is probably a case of dermatitis herpetiformis-like eruption in a child, but there have been reported some very inflammatory, widespread cases of creeping eruption, and I would not be satisfied until treatment for creeping eruption had been given this child.

DR. TRAUB: We have had a good many very valuable suggestions for diagnosis. The fact that the patient has had adequate dosage of antibiotics

and sulfonamides certainly seems to be against the diagnosis of dermatitis herpetiformis and/or an infectious process by itself. My first thought—and that is the reason I asked this patient carefully about drugs—is that I felt this might be either penicillin eruption or iodide eruption in a child. But then I also recalled having had a youngster with erythema multiforme-like eruption that I passed off rather lightly at the University Hospital in Burlington, and subsequently the child developed a very typical Hodgkin's disease. That cannot be entirely excluded in a patient of this sort.

I think Dr. Andrews' suggestion is an excellent one, except for one thing. Certainly, the local people down there would have thought of that first (creeping eruption) and would have fairly well ruled it out in the beginning.

DR. SACHS: Dr. Nelson showed me the slide. It suggested a toxic subepidermic bullous lesion. I did not think it was dermatitis herpetiformis or erythema multiforme. I have not seen ordinary pemphigus, which I thought this slide showed, in a child 3 years old. Having now seen the child and the slide, I should suggest the possibility of some nevoid condition in the abdomen or kidney or some anomaly in the kidney, because of this pemphigus-like eruption.

DR. CIPOLLARO: Since various diseases have been mentioned as diagnostic possibilities, I should like to bring to your attention that Dr. Nelson, in his history, emphasized the fact that this child has had a white cell count of up to 39,000 and has had up to 69% lymphocytes. Somebody also brought out the fact that this child has splenomegaly and hepatomegaly. Also, the bone morrow findings were negative, and there were 8% to 10% eosinophils.

I do not think this child has lymphoblastoma, but I cannot rule out the possibility of lymphoma. Secondly, I should like to bring to your attention that dermatitis herpetiformis is not the simple, clear-cut disease that is so graphically described in our textbooks. It is a protean disease. It has many and varied clinical manifestations. I cannot help feeling that this child, particularly with the history that at the beginning there was a generalized pyogenic eruption (which gave some doctor the idea that the child might have impetigo), may have had Duhring's disease. That unusual form of Duhring's disease, which is now subcorneal pustular dermatitis, usually begins with an eruption generally diagnosed as pyoderma. The three cases I sent to Dr. Costello for study and treatment all began with pustular eruptions, pyogenic-like, and then developed lesions which gradually developed into this unusual form of Duhring's disease.

DR. NELSON: I should emphasize that the 25,000 to 39,000 white blood cell count occurred while the child was in the hospital and very febrile, with pustular skin lesions.

I do not think anything more need be said, except to thank the members for their very erudite discussion, which I shall transmit to Dr. Van Velsor and Dr. Callaway.

Diagnosis: Tuberculous Ulcer of the Leg?

Presented by DR. LESLIE P. BARKER.

The patient was a 53-year-old Negro housewife.

History: The patient was first seen in 1938, with a granulomatous lesion of the upper lip, tip of nose, and both nares. Clinically, the lesion was thought to be syphilis, but serological tests were all negative; also, x-ray pictures of the lungs and a complete blood work-up were normal. She was given a course of arsphenamine and bismuth, but the lesion required many months to heal.

Since that time, she has had several large ulcerations of the legs similar to the present lesion that began as a subcutaneous nodule. The ulcers healed only after hospitalization. The present lesion began about eight months ago, as a subcutaneous nodule that ulcerated, and the ulcer enlarged to its present size.

Examination: On the anterolateral aspect of the left leg just below the knee is a large kidney-shaped ulcer about 6×4 in. in size. The borders are slightly undermined with deep red, slightly elevated skin margins. The base of the ulcers showed bright red granulations with islands of new epithelium. Several large irregular-shaped scars are present on the leg as a result of previous lesions.

Laboratory tests: Roentgenograms of chest, sinuses, and leg, normal. Serologic tests for syphilis, including TPI, negative. O.T. was positive, 1:10,000 dilution. Cultures of the lesion for deep fungi, negative. Guinea pig inoculation, results not reported.

Biopsy: Biopsy specimen from the margin of the ulcer was nonspecific but suggested a tuberculous granuloma.

The lesion failed to heal with local antibiotic therapy, and she was hospitalized and given isoniazid and streptomycin internally. There has been a slow but gradual healing of the lesion. It is questionable whether the drugs or bed rest were responsible for the improvement.

Discussion

DR. SACHS: In view of the positive tuberculin test, the more or less positive biopsy specimen, and also the resistance to antisyphilitic therapy, one would probably have to accept the diagnosis of granuloma. However, clinically, I should still think of a syphilitic process and, instead of giving her the type of antibiotic treatment she has had, I should like to see what would happen with the old-fashioned mixed treatment for a few weeks.

DR. TRAUB: I agree with the diagnosis of tuberculous lesion completely. The way this started, at the nose, I think, is quite characteristic. I have seen a number of these patients, and one could almost interchange the photographs of this original nose lesion. When Dr. Barker showed me the photograph, I knew I had seen this woman. She had been at the skin and cancer clinic years ago, and she had been suspected of being and was treated for syphilis but had tuberculosis.

DR. COSTELLO: I do not think she has tuberculosis. I never saw that disease to leave a scar of this character. I think it is dermatitis gangrenosa, and it may last for years.

DR. NELSON: I am interested in the patient's past history of granulomatous lesions of the nose and upper lip. Probably, the present lesion has the same etiology, and I think that we should persevere with the tuberculostatic drug. Perhaps this is a situation where calciferol might be added.

DR. ANDREWS: I feel as Dr. Nelson does. The involvement of the upper lip looks to me like macrocheilia, caused by tuberculous lymphangitis. I think the response in the hospital to the antitubercular drugs and rest was indicative. That is the kind of treatment this woman should have. Macrocheilia granulomatosa of Meischer should be ruled out by biopsy.

DR. MILLER: I think we are forced to accept the diagnosis of tuberculosis. The patient has been studied very thoroughly twice and the conclusion has been the same both times, with all the other things ruled out.

DR. CIPOLLARO: You do not think she has syphilis?

DR. MILLER: I thought so originally.

DR. CORMIA: This may seem like a contradiction, but I should agree with both Doctors Traub and Costello. Primarily, this condition is tuberculosis. I think, also, superimposed on the tuberculosis, she has some infection and probably an element of stasis as well. She should be treated not only for tuberculosis but also for infection, and supportive therapy be given to the leg.

DR. BARKER: I am not completely satisfied with a diagnosis of tuberculosis in this patient. I think that pyogenic gangrenosum must be ruled out. While in the hospital she was given isoniazid and streptomycin. I do not believe she responded any better than if she had been treated by bed rest alone.

Lupus Erythematosus: Discoid Type with Extensive Mouth Lesion. Presented by DR. DOUGLAS TORRE.

Hansenosis (Tuberculoid Type): Malum Perforans. Presented by DR. MAURICE J. COSTELLO.

For Diagnosis: Discoid Lupus Erythematosus? Presented by DR. J. LOWRY MILLER.

PHILADELPHIA DERMATOLOGICAL SOCIETY

Herman Beerman, M.D., Chairman
Herbert A. Luscombe, M.D., Secretary

Nov. 21, 1958

Acrosclerosis with Calcinosis: Congenital Duplication of Right Renal Pelvis and Ureters with Partial Obstruction. Presented by DR. DONALD M. PILLSBURY and (by invitation) DR. CHARLES MESSENGER and DR. WILLIAM GERSTEIN.

Pachyonychia Congenita. Presented by DR. DONALD M. PILLSBURY and (by invitation) DR. R. FLORENCE.

Polyostotic Fibrous Dysplasia (Albright's Disease). Fracture of the Head of the Left Femur. Presented by DR. DONALD M. PILLSBURY and (by invitation) DR. A. MESSENGER and DR. J. HARUN.

Submitted for publication Feb. 16, 1959.

1. Chronic Alcoholism. 2. Porphyria Cutanea Tarda. Presented by DR. NORMAN R. INGRAHAM, DR. GEORGE W. HAMBRICK JR., and (by invitation) DR. GEORGE LUDWIG and DR. C. AARONSON.

1. Acanthosis Nigricans. 2. Diabetes Mellitus, Insulin-Resistant. 3. Amenorrhea, Cause Undetermined. Presented by DR. DONALD M. PILLSBURY and (by invitation) DR. ROBERT L. EPPS.

SAN FRANCISCO DERMATOLOGICAL SOCIETY

R. Raymond Allington, M.D., President
Ralph T. Behling, M.D., Secretary
Herbert L. Joseph, M.D., Editor

Jan. 16, 1959

Case for Diagnosis: Psoriasis; Chronic Radiodermatitis? Angiomas of Amputation Stump vs. Kaposi's Hemorrhagic Sarcoma. Presented by DR. EUGENE M. FARBER and DR. JAMES B. PETERSON (by invitation).

A 67-year-old man has had psoriasis for 43 years. About 33 years ago he received x-ray treatment to the limbs. Radiodermatitis subsequently developed on the lower extremities. In 1950, a squamous-cell carcinoma of the right shin developed for which a right supracondylar amputation and radical inguinal lymph node dissection was done. The nodes showed no evidence of tumor.

Since 1951 numerous red, infected, ulcerated lesions have developed on both lower extremities. One was removed from the left knee in 1951 and four from the left leg in 1955. Many recurrent lesions have developed on the stump along the incision line. An excision and graft were done in this area in 1955, in 1956, and again in 1957. Lesions have continued to develop on the stump and have been resected repeatedly until July, 1958, when a right hip disarticulation was done. A skin flap was swung in from the posterolateral hip, where good nonirradiated skin was available. All of the lesions removed were interpreted to be angiomas or pyogenic granulomas histologically.

In the past four months, the stump again has developed an enlarging, firm, tender plaque-like lesion.

The skin on the left leg is telangiectatic, atrophic, hyperpigmented, depigmented, and hairless. Lesions of psoriasis and small keratoses stud this area. On the anterior left upper thigh is an irregular 9×5 cm., oval, erythematous, indurated plaque with a 1 cm. central scaly nodule.

The amputation stump contains an irregular, 10×12 cm., violaceous, indurated lesion in the closure line. It appears cyanotic, and there is a bloody discharge.

There are also postradiation changes on the backs of the hands, in which are many keratoses. Typical lesions of psoriasis are present on the elbows, left knee, and sacrum.

Discussion

DR. RICHARD SKAHEN (by invitation): The nuclei of the endothelial cells and haphazard distribution of the vascular channels certainly suggest a malignancy. One area of the slide showed good sheet-like proliferation of the endothelial cells. I believe this is Kaposi's hemorrhagic sarcoma.

DR. ALVIN COX (by invitation): This is a highly proliferative vascular lesion and histologically borders on malignancy. I do not believe the sheet-like cells are quite as characteristic of Kaposi's as I have seen but assume it to be this until there is evidence to the contrary.

DR. WILLIAM S. LEVY: Dr. Gilbert Bierne and I have been doing work on amputees for approximately four years. We described the "stump edema syndrome" occurring under suction sockets. This results from alternating positive and negative pressures. Biopsy specimens from some of these lesions showed hemorrhagic changes in small nodules which were essentially benign granulating lesions with thin-walled blood vessels, much as seen in this case. In our patients, prolonged external compression produced gradual disappearance of the lesions.

It is also interesting to note that there are keratotic lesions on the palms and soles, indicating that probably he has had arsenic at some previous time.

DR. PAUL CROSSLAND: Patients such as this, who have received considerable x-ray therapy in the past, might be a source of information regarding mutations. Undoubtedly, this patient has received considerable x-ray to the gonads, but his two sons were 11 and 12 years old at the time the x-ray was given.

Useful information would be obtained if there were a method of central reporting of persons irradiated before having children. By tracing the children, grandchildren, and subsequent generations, information regarding the mutative effect of x-ray could be accumulated.

DR. EUGENE FARBER: This man poses an urgent problem. The surgeons would like to do a hemipelvectomy as soon as possible because they feel that with further delay there will not be enough good skin to close. Certainly, if the proliferative reaction spreads to involve a larger area, they will not have enough skin.

I have observed this patient for almost eight years. He has had three amputations, and with a fourth the same problem will probably remain. He is now at the point of no return.

This proliferative tissue looks like a bunch of heavily piled up crusted material, and, when it is cut into, fresh blood is obtained. I have done this several times. Secondary infection occurs periodically. Is this proliferative reaction a sequela to the x-ray given years ago? I cannot be certain, but the proliferative reaction is occurring in skin which apparently has not been x-rayed as well as that which has been irradiated.

It has been suggested that there might be an underlying deep squamous-cell carcinoma blocking the lymphatics that our biopsies have not been deep enough to show. I have never seen Kaposi's sarcoma begin with a subcutaneous infiltrating mass. I wonder about the possibility of incompetency in the pelvic veins and veins in the short stump with back-flow and resultant edema and breaking down of the skin. This, with secondary infection might explain the reaction as inflammatory rather than neoplastic.

I hope you will not be too critical with my final suggestion, but, in order to save this man from radical surgery, perhaps x-ray therapy should be given to the stump.

Addendum: A higher amputation has since been done, and there is another recurrence in the stump.

Benign Cystic Epithelioma. Presented by DR. HERMAN V. ALLINGTON.

A 21-year-old man began to develop small tumors on the face at the age of 2 years. They have continued to appear in this area ever since. Six "cysts" were removed from the maxillary and mandibular areas at the age of 7 years. He states

that these contained cheesy material and abnormal teeth. A breast tumor the size of a golf ball was removed at the age of 15 years and said to be benign. At age 17 years a thyroglossal duct cyst was removed and subsequently reexcised after recurring.

Hundreds of lesions have been taken off the face by Dr. George K. Rogers of Phoenix, Ariz. A pathology report from these is basal-cell carcinoma, and one had been growing rapidly.

The lesions are primarily on the central portion of the face, brows, and cheeks, with a few scattered over the upper trunk. They vary from pinpoint to 1 cm. in diameter and are semitranslucent, smooth, skin-colored to pinkish nodules and papules.

There are healing wounds on the right side of the face, where multiple lesions were removed by electrodesiccation and curettage eight days ago. One on the inner canthus of the left lower eyelid and one in the right nasolabia were found to be infiltrating very deeply.

Discussion

DR. ALBERT KLIGMAN: We do not have a suitable name for this condition, but it is a genuine entity. Pathologically, certainly it is a basal-cell epithelioma, but it does not follow the same clinical pattern but has multiform characteristics. One sees various types of hamartomatous growths, deviations, and variations of structure. In our experience they are entirely benign and do not become typical rodent ulcers. I believe they can be treated rather conservatively. This appears to be a hereditary condition which is usually an incomplete dominant, passing on in a faulty way in the family.

DR. WILLIAM S. LEVY: I believe this case falls into the general classification of multiple benign cystic epithelioma. Malignant degeneration sometimes occurs in these lesions. As Dr. Kligman pointed out, the malignant degeneration is not the typical rodent type but a rather benign and slow proliferation into the dermis.

DR. HERBERT L. JOSEPH: I see no objection to the name epithelioma adenoides cysticum for this condition and believe it is a distinct entity. The term multiple benign cystic epithelioma is misleading, as they do not always remain truly "benign." In 1955, I presented a patient with this condition to this society, a 40-year-old man with a typical rodent ulcer on the right chin (A.M.A. ARCH. DERMAT. 74:113, [July] 1956). A photograph of this patient was published and the carcinoma is readily seen. This patient had two brothers with the condition and a sister without.

DR. ARNE INGELS: I should also like to emphasize the great variation in the histopathological picture in this disease. It may look like a trichoepithelioma, seborrheic verruca, or hamartoma, or it may be adenoid.

DR. HERMAN ALLINGTON: Two of the lesions I took off were invasive in the same way as ordinary rodent ulcers. Each lesion should be considered as potentially invasive. This patient has had hundreds of lesions removed. All that could be seen were supposedly taken off 11 months ago. Those now present have developed since then. Both the patient and his mother feel that if they were not treated, they would increase rapidly in size and they would quickly require removal. Thus, I do not believe they can be entirely neglected. I have been considering a trial of skin grafting in the central areas of the face.

The other defects, including thyroglossal duct cysts, maxillary and mandibular lesions, and the breast tumor, are all probably manifestations of the basic defect. This patient seems to be intelligent and well oriented, through he speaks as though he might have some mental retardation. There is no family history of similar involvement.

Lepromatous Leprosy. Presented by DR. PAUL FASAL.

Leprosy (Borderline Type). Presented by DR. PAUL FASAL.

Lepromatous Leprosy. Presented by COL. RAYMOND M. WILLIAMS, (MC), and CAPT. ALBRECHT F. J. SOMMER, (MC), U.S. Army (by invitation).

Monilethrix. Presented by CAPT. ROBERT A. NEILL, (MC), U.S. Army (by invitation).

Reticulum-Cell Sarcoma with Skin Metastases. Presented by DR. EUGENE M. FARBER and DR. THOMAS J. SULLIVAN (by invitation).

Abstracts from Current Literature

THE BIOLOGICAL EFFECTS OF VANADIUM. CHARLES E. LEWIS, A. M. A. Arch. Indust. Health 19:497-503 (May) 1959.

A sign seen in 37% of 24 vanadium workers studied for irritation referable to vanadium dust was a green coloration of the tongue. Irritation of the eyes, nose, throat, and respiratory tract was seen in 62% of these workers.

LAZAR, Chicago.

CANCER OF THE SCROTUM IN WAX PRESSMEN. J. G. LIONE and J. S. DENHOLM, A. M. A. Arch. Indust. Health 19:530-539 (May) 1959.

The incidence of scrotal cancer among wax pressmen with 10 or more years of service was significantly higher than in the general population. New lesions may occur many years after cessation of contact with crude petroleum wax. Personal hygiene, education of workmen, and protective clothing are the basis of a protective program.

LAZAR, Chicago.

KERATOMYCOSIS. DAVID BARSKY, A. M. A. Arch. Ophth. 61:547-552 (April) 1959.

The author reports six cases of fungus infections of the cornea which led to enucleation. Clinical diagnosis was made only once, but the fungus was demonstrated in each case by microscopic examination.

Keratomycosis is usually secondary to a foreign-body injury and the use of antibiotic-corticosteroid preparations for corneal ulcers is contraindicated. In one quoted study, the incidence of fungus keratitis in cortisone-treated eyes was 80%, in contrast to 20% incidence in the control group.

LAZAR, Chicago.

RHINOPHYMA. FRANK E. FISHOF, A. M. A. Arch. Otolaryng. 69:424-430 (April) 1959.

Repair of a case of rhinophyma is reported. The development of the rhinophyma-rosacea inferiority complex is described, the evolution of the condition traced, and therapy discussed.

LAZAR, Chicago.

METASTASIZING SWEAT-GLAND CARCINOMA. Y. G. JACOBSON, T. D. REES, R. GRANT, and V. H. FITCHETT, A. M. A. Arch. Surg. 78:574-581 (April) 1959.

A primary carcinoma of sweat-gland origin occurring on the cheek metastasized to the right cervical chain of lymph nodes. One patient previously reported died with widespread metastases 30 years after the onset of the tumor.

LAZAR, Chicago.

A FATAL GRANULOMATOUS DISEASE OF CHILDHOOD. R. A. BRIDGES, H. BERENDES, and R. A. GOOD, A. M. A. J. Dis. Child. 97:387-408 (April) 1959.

A new syndrome, consisting of chronic suppurative lymphadenites, hepatosplenomegaly, pulmonary infiltrations, and eczematoid dermatitis, in four boys is described. The generalized process is a granulomatous one associated with hypergamma globulinemia. Extensive clinicopathological and laboratory examinations did not uncover the nature of the syndrome. Therapy was without effect on the process, which progresses relentlessly.

LAZAR, Chicago.

CASE OF KAPOSI'S SARCOMA WITH SOFTENING OF THE NODULES AND BONE CHANGES. L. BESSONE and C. GIACOMETTI, Ann. ital. Derm. Sif. 12:431-461 (Nov.-Dec.) 1957.

This is an interesting discussion on the gradual softening ending in fluidification of the nodules and on bone involvement in Kaposi's sarcoma.

RONCHESE, Providence, R. I.

BEHAVIOR OF GLUTAMINIC ACID-PYRUVIC ACID-TRANSAMINASE OF BLOOD SERUM AND CUTANEOUS BLISTER FLUID IN ECZEMA AND BULLOUS DERMATOSES. G. WEBER and H. THEISEN, Arch. klin. u. exper. Dermat. 208:93-97, 1959.

Determinations of glutaminic acid-pyruvic acid-transaminase of blood serum and fluid of spontaneous and cantharidin blisters of the skin in 29 patients with eczema, dermatitis, and

bullous dermatoses revealed no distinct differences of enzyme activity except in a case of diabetes with intertriginous eczema. No conclusion could be drawn whether this aminopherase originates in human epidermis or diffuses into the blister from the blood circulation.

HOLLANDER, Springfield, Mass.

HYPEREOSINOPHILIA SYNDROME WITH SPECIFIC SKIN CHANGES (EOSINOPHILIC LEUKEMOID). L. PFLEGER and J. TAPPEINER, Arch. klin. u. exper. Dermat. 208:98-115, 1959.

According to the author, this is the first case of eosinophilic leukemoid with skin changes. A married woman, 46 years of age, had been affected for about 20 years with generalized papular eruption and enlargement of lymph glands. In 1952, she first had erythematous edema of the orbital-, lid-, and perioral regions with inflammatory infiltration of the left corner of the mouth. There also was a generalized papulocrustosquamous eruption. Diagnosis of prurigo eczematosa with secondary pyoderma was made. She had several flare-ups since 1952, consisting of tumorous skin lesions of the face particularly and generalized papular and nodular lesions. There was enlargement of the liver. Blood eosinophilia was up to 70% with leukocytosis up to 23,000. Bone marrow revealed marked increase of eosinophilic granulocytes. Histologic examination of skin lesions and lymph glands showed reticulohistiocystic infiltrates with numerous eosinophilic granulocytes. Steroid therapy brought about improvement but no permanent cure. Prognosis is favorable quoad vitam. Pathogenesis is based on an allergic reaction in a hyperergic organism which constitutionally tends to development of hypereosinophilia.

HOLLANDER, Springfield, Mass.

DOLICHOSTENOMELIA (MARFAN SYNDROME) AND ECTODERMAL DYSPLASIA. W. ADAM and H. W. KELLING, Arch. klin. u. exper. Dermat. 208:116-127, 1959.

Observation of dolichostenomelia in two females of 19 and 23 years of age. In one case, there were disseminated verrucae vulgares and nevi verrucosae, resembling histologically angiokeratoma. The other case showed linear pigmentations of the right upper arm, striate distensae of hips and thighs, and keratosis pilaris of buttocks and extremities. These skin changes may represent symptoms of the Marfan syndrome.

HOLLANDER, Springfield, Mass.

CONTRIBUTION TO THE PROBLEM OF PYODERMA ULCEROSUM. H. KRESBACH, Arch. klin. u. exper. Dermat. 208:128-159, 1959.

This is a description of a case of pyoderma ulcerosum in a 34-year-old woman. Fibrinous cystitis also existed with the presence of Bacillus proteus vulgaris in the urine. Examination of the ulcers of the skin showed a mixed flora of Pseudomonas pyocyaneus, Proteus vulgaris, Staphylococcus aureus hemolyticus, and Streptococcus pyogenes hemolyticus. Injections of various cultured bacteria into guinea pigs and mice did not show any pathogenicity. Different skin tests with bacterial suspensions and bouillon culture filtrates, as well as experiments on guinea pigs for antigenic properties were negative. A study of the literature makes the author believe that pyoderma ulcerosum with or without ulcerative colitis, described under various names, represents so far a clinicomorphologic entity. Bacteriologic findings do not permit an etiologic diagnosis. A nonspecifically increased reactivity of the skin organ plays a role in the pathogenesis of pyoderma ulcerosum.

HOLLANDER, Springfield, Mass.

DIFFERENT BEHAVIOR OF VARIOLA-VACCINIA-ANTISERA ON PRECIPITATION IN DOUBLE-DIFFUSION TEST. W. ROHDE and O. KÜHN, Arch. klin. u. exper. Dermat. 208:160-173, 1959.

Variola-vaccinia antigens from various laboratories (Berlin, Bern, Moscow, and Hanoi) were examined for their specific antigenic qualities. The agar-diffusion test is specific and usable in qualitative form for the diagnosis of variola.

HOLLANDER, Springfield, Mass.

ISOLATED FOLLICULAR DYSKERATOSIS. W. NIKOLOWSKI, Arch. klin. u. exper. Dermat. 208:174-180, 1959.

In re-examining the histologic slides of skin cancers of the last 12 years from the skin clinic of Tübingen only one case of isolated follicular dyskeratosis was found. It was a cutaneous horn-like lesion of match-head size of the left upper eyelid in a 61-year-old man, which on original histologic examination was diagnosed as early epidermoid carcinoma.

HOLLANDER, Springfield, Mass.

CONTRIBUTION TO ETIOLOGY OF LIGHT DERMATOSES. H. LANGHOF and G. SCHNEIDER, Arch. klin. u. exper. Dermat. 208:181-191, 1959.

Spectroanalytic measurements of light transmission were done in early spring on 17 specimens of epidermis from the extensor aspect of the forearm. Biopsies by punch under ethyl chloride spray were performed on nine persons with light dermatoses and on seven with normal skin. Except for two cases of xeroderma pigmentosum with increased light transmission, none of the other cases showed abnormal light transmission. Chromatographic analysis of amino acids of these epidermis specimens revealed a large quantity of phenylalanine. In four cases of cutaneous porphyria a large quantity of tyrosine was found in the epidermis but no methionine and phenylalanine.

HOLLANDER, Springfield, Mass.

CATHEPTIC ENDOPEPTIDASE IN NORMAL HUMAN SKIN AND DERMATOSES. G. STÜTTGEN and I. WÜRDEMANN, Arch. klin. u. exper. Dermat. 208:192-203, 1959.

Ultraviolet-spectrophotometric and colorimetric examinations of 6 specimens of normal skin, 11 of various dermatoses, and 5 of skin tumors revealed an alkaline dermoprotease and a catheptic acid endopeptidase. There was increased activity of endopeptidases of the skin in eczema and psoriasis.

HOLLANDER, Springfield, Mass.

INFLUENCE OF SERUM AND ITS FRACTIONS ON ENDOPEPTIDASES OF HUMAN SKIN. G. STRÜTTGEN, H. WÜST, and K. ORFANOS, Arch. klin. u. exper. Dermat. 208:204-213, 1959.

Serum and its fractions may influence endopeptidases of the skin differently. Acid milieu usually causes activation of protolysis.

HOLLANDER, Springfield, Mass.

SIGNIFICANCE OF HISTAMINOPEXY IN DERMATOLOGIC RESEARCH. P. WODNIANSKY and H. TIRSCHEK, Arch. klin. u. exper. Dermat. 208:214-222, 1959.

Examinations of histaminopexy were made on serum of 99 persons with various dermatoses. Lack or decrease of histaminopexy probably represents a hereditary symptom of allergic constitution. No definite conclusions could be drawn from these examinations. There was lack of histaminopexy in 15 children with infantile eczema and 6 of their parents. Subcutaneous injection of homeoserum in 17 patients with atopic dermatitis and lack of histaminopexy produced some increase of histaminopexy and improvement of skin symptoms. Homologous serum hepatitis developed in four patients who had received these injections.

HOLLANDER, Springfield, Mass.

PORPHYRIA CUTANEA TARDA. H. IPPEN, Arch. klin. u. exper. Dermat. 208:223-259, 1959.

Clinic, diagnosis, differential diagnosis, histology, therapy, and prognosis of porphyria cutanea tarda are discussed in detail. Thirty-one own cases were observed between 1956 and 1958. The appropriate literature is reviewed. Porphyria cutanea tarda usually develops in persons over 50 years of age. There are no abdominal or central nervous system symptoms. Skin changes, such as blister formation on parts exposed to sunlight, milia, hyperpigmentations, and scleroderma-like changes predominate. There is no specific therapy. The author prefers therapy with crude mashed liver.

HOLLANDER, Springfield, Mass.

ERYTHEMA ELEVATUM DIUTINUM, GRANULOMA ANNULARE, NECROBIOSIS LIPOIDICA, AND GRANULOMATOSIS DISCIFORMIS GOTTRON-MIESCHER. COMPARATIVE FREQUENCY-ANALYTIC STUDY. H.-J. HEITE and H. X. SCHARWENKA, Arch. klin. u. exper. Dermat. 208:260-290, 1959.

One hundred cases of erythema elevatum diutinum, 430 of granuloma annulare, 232 of necrobiosis lipoidica, and 63 of granulomatosis disciformis are reviewed from the literature concerning their distinctive features, sex and age distributions, and localization. The Bury type of erythema elevatum diutinum is closely related to Gr. A., while the Hutchinson type of E. El. D. can definitely be distinguished. Granuloma annulare in contrast to necrobiosis lipoidica and granulomatosis disciformis is found more in females. The legs are the favorite localization of necrobiosis lipoidica without diabetes and granulomatosis disciformis in contrast to necrobiosis lipoidica with diabetes and granuloma annulare.

HOLLANDER, Springfield, Mass.

ATYPICAL ERYTHEMA NODOSUM. B. BÄFVERSTEDT, Arch. klin. u. exper. Dermat. 208:291-300, 1959.

This article is a description of four cases of an erysipelas-like eruption of the legs which, in the author's opinion, represents atypical erythema nodosum. Histologic examination was compatible with erythema nodosum. Streptococci or sarcoidosis may play a role in the pathogenesis of these cases.

HOLLANDER, Springfield, Mass.

CONTRIBUTION TO THE PROBLEM OF LICHEN MYXEDEMATOSUS. K. A. v. ZEZSCHWITZ, Arch klin. u. exper. Dermat. 208:301-316, 1959.

A waxy, papular eruption of the trunk and extremities of four years' duration in a 57-year-old woman is described. Clinically, it resembles eruptive collagenosis, described by J. Gay Prieto. Histologically, the middle and deeper parts of the cutis show circumscribed areas of separated and rarefied collagenous bundles. Toluidine-blue staining reveals distinct metachromasia. The skin lesions disappeared under prednisone therapy but recurred two weeks after cessation of steroid medication.

HOLLANDER, Springfield, Mass.

EFFECT OF ENZYME INHIBITORS ON HAIR GROWTH IN RATS. O. BRAUN-FALCO and H. THEISEN, Arch. klin. u. exper. Dermat. 208:317-324, 1959.

Intradermal injections of enzyme inhibitors caused circumscribed reversible loss of hair in rats. Regrowing hair was free of pigment first. This could be an effect of the enzyme inhibitors on the tyrosinase system. Examinations suggest that a temporary metabolism disturbance in hair matrix cells due to inhibitory influences on enzymes or enzyme systems could be responsible for the development of temporary alopecias in man.

HOLLANDER, Springfield, Mass.

OCCUPATIONAL LEUKODERMA. EWAN MURRAY-WILL. Australian J. Dermat. 4:210-212 (Dec.) 1958.

Occupational leukoderma due to contact with acrylic denture material containing monobenzyl ether of hydroquinone is reported.

LAZAR, Chicago.

GRANULOMATOSES DISCIFORMIS CHRONIA ET PROGRESSIVA (MEISCHER). F. J. COLLETT and V. J. McGOVERN, Australian J. Dermat. 4:213-215 (Dec.) 1958.

A case similar to sarcoidosis histologically and similar to necrobiosis lipoidica clinically but fitting neither condition is reported. The author believes the condition to be that reported by Meischer and Leder.

LAZAR, Chicago.

HEINZ-BODY ANEMIA DUE TO DAPSONE. R. S. SMITH and SUZANNE ALEXANDER, Brit. M. J. 1:625-627 (March 7) 1959.

Heinz bodies are small refractile granules found in the red blood cells in many cases of drug hemolytic anemia. Using a supravital stain, Heinz bodies are readily demonstrated and are useful in the supervision of patients taking diaminodiphenyl sulphone (Dapsone) for dermatitis herpetiformis. Four cases showed the formation of Heinz bodies, and three of these developed hemolytic anemia.

LAZAR, Chicago.

HERPES ZOSTER DURING STEROID THERAPY. J. S. CREIGHTON and W. A. DEWAR, Brit. M. J. 1:648-649 (March 7) 1959.

Corticotrophin in a dosage of 40 I. U. gel daily for 20 days did not prevent the appearance, alter the course, or the associated pain of herpes zoster. No aggravation of the infection occurred either.

LAZAR, Chicago.

ADULT LEUKEMIA. W. M. COURT BROWN and R. DOLL, Brit. M. J. 1:1063-1069 (April 25) 1959.

Deaths from leukemia in England and Wales for the period 1945 to 1947 were studied and classified. Three types were noted; acute leukemias of all types, chronic myeloid leukemia, and

chronic lymphatic leukemia. Three times, 1945 to 1949, 1950 to 1954, and 1955 to 1957 were used with the age and sex of each person noted.

The data accumulated indicate an increase in the incidence of acute leukemia. Such a conclusion is compatible with the concept that ionizing radiation plays some role in the changed incidence of the disease.

LAZAR, Chicago.

RADIATION AND LEUKEMIA. EDITORIAL, Brit. M. J. 1:1095 (April 25) 1959.

In commenting on the article by Drs. W. M. Court Brown and R. Doll, the editorial reflects that the mortality from chronic lymphatic leukemia over the age of 60 is due to better recognition of these diseases in the elderly. Observed increases in death rates from acute leukemia at ages under 60 are largely real and due to increasing exposure to leukemogenic factors in the environment. Below age 60, the increase is primarily due to acute leukemia and to a small extent to chronic myeloid leukemia—"the forms of the disease which radiation is known to induce."

LAZAR, Chicago.

ACRODERMATITIS CHRONICA ATROPHICANS. R. CAVALIERI, Cronache I. D. I. 12:30-37 (Feb.) 1958.

From the study of two cases of acrodermatitis chronica atrophicans, Cavalieri concludes that trauma and frost bite in northern climates are elective factors in its development. The disease is infectious and antibiotics are effective.

RONCHESE, Providence, R. I.

SUBCUTANEOUS CYSTICERCOSIS. JOSÉ H. FRENKEN, Dermatologia (México) 2:3-18 (Dec.) 1958.

The patient presented about a dozen round subcutaneous tumors covered with healthy skin in the left temporal region, in the nape, and in the thorax. They were of various size but ranged between that of a pea and a hazelnut. They were firm, painless, and movable on the subjacent tissues. A biopsy specimen showed skolex of Taenia solium. An extensive bibliography is given.

DERBES, New Orleans.

CHROMOBLASTOMYCOSIS. JOSEFA NOVALES, Dermatologia (México) 2:30-36 (Dec.) 1958.

This article presents a case treated with fair results with diamino-diphenyl-sulphone.

DERBES, New Orleans.

INFANTILE LEPROSY. AMADO SAUL, Dermatologia (México) 2:45-55 (Dec.) 1958.

A case of infantile tuberculoid leprosy is reported in a child of three and one-half years. The incubation period in this case is clear: the infecting case arrived at the house in April, 1953, the child was born Sept., 1954, and began to be ill in Sept., 1956, i. e., at two years of age, the intimate contact having begun at eight months of age, thus the incubation period is 18 months more or less. Of further interest is the fact that this child was the only member of the family who contracted leprosy, although the infecting person was exposed to the entire family.

DERBES, New Orleans.

CUTANEOUS OPPENHEIM-URBACH DYSLIPOIDOSIS. M. PISANI, Dermatologia (Napoli) 9:147-155 (May) 1958.

In two adult diabetic women the dermatosis was scleroderma-like. In a third one, the appearance was granuloma annulare-like. The disorder is considered a dyslipoidosis from hepatopancreatic dysfunction.

RONCHESE, Providence, R. I.

BURNS (THERMODERMATITIS). M. COMÈL ET AL., Minerva dermat. 33:105-161 (Jan.-March) 1958.

Burns in Europe are still the domain of dermatology. Comèl and his pupils, Mian, Robba, and Grassi offer an extensive dissertation on theory and practice of burns. Epidemiology and clinic are discussed. A large part of the paper is devoted to therapy.

RONCHESE, Providence, R. I.

MELANOBLASTOMA IN ALBINO. R. LEONARDI and S. GRASSO, Minerva dermat. 33:24-26 (Jan.) and 306-308 (Aug.) 1958.

This is the 3rd case reported in the literature of a melanoblastoma developing in the albino. It showed nuclei with filaments peculiarly radiating like the rays of a wheel. A similar observation was made by Masson. The authors examined 30 cases of melanoblastoma from their files and found the nuclear peculiarity in 11 cases or in 36.60% and particularly in the amelanotic type.

RONCHESE, Providence, R. I.

LUPUS ERYTHEMATOSUS PROFUNDUS. N. A. GUIMARAES, Minerva dermat. 33:295-304 (Aug.) 1958.

A review and discussion of the literature and report of two cases in which peculiar alterations of the striated muscles were found.

RONCHESE, Providence, R. I.

Books

Current Problems in Dermatology. Vol. 1. Edited by R. Schuppli. Price, 48 Swiss francs. (For subscribers to *Dermatologica,* 43 Swiss francs.) Pp. 530, with 98 illustrations. S. Karger, AG., Arnold Böchinstrasse 25, Basel, 1959.

This is intended to be the first in a series of volumes on current problems in dermatology. It will keep the reader abreast of the latest work in the fields covered. It does this excellently in the present volume, giving a bibliography which covers recent work through 1957. With the exception of the chapters by F. Blank on the isolation and classification of Dermatophytes, that by M. Reuter on necrotizing angiitides, and the one by Dostrovsky, Sagher, and Cohen on pemphigus vulgaris under prolonged massive treatment with corticotropin (ACTH) and steroids, which are in English, all the other chapters are in German. The subjects covered include physiology of the skin, the autonomic nervous system and the skin, various manifestations of allergy, vasculitis, reticuloses, porphyrins, radioactive isotopes, and new drugs. The authors are outstanding in their fields. This first volume can be highly recommended.

The Year Book of Dermatology and Syphilology (1958-1959 Year Book Series). Edited by Rudolph L. Baer, M.D., and Victor H. Witten, M.D. Price, $6.50. Pp. 477, with 57 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1959.

The latest "Year Book" is an altogether worthy addition to this long-established, invaluable series of reviews. The leading article in this edition is concerned with benign, pigmented lesions. Written succinctly, it is a readable discussion and most appropriate in these days of cancer consciousness. Both generalists and specialists will find the material authoritative, well-documented, decisive, and yet restrained and with fairness shown to the various disciplines that treat such lesions. The selection of articles was careful and most of the abstracts were done expertly. More numerous than in past issues are the comments which are both provocative, well-considered, and accurate. The "Year Book" continues to serve as a valuable review and reference work for everybody interested in dermatology.

The Nursing and Management of Skin Diseases. By D. S. Wilkinson, M.D., M.R.C.P. Price, $5.75. Pp. 288. The Macmillan Company, 60 5th Ave., New York 11, 1959.

It is obvious that results from therapy for skin diseases and the associated disability or discomfort are often directly related to the type of nursing care and management of such disorders. Few nurses and even few physicians are sufficiently skilled to treat dermatologic disorders, and it is to them that Dr. Wilkinson has directed his book, which is an excellent, clear, simple, and practical reference work. Special dressings, office procedures, topical remedies, dermatological emergencies, and general principles of management are discussed. The illustrations, though not numerous, are well selected and instructive. The descriptions of diseases are rather brief for dermatologists but altogether adequate for nurses and nondermatologists. This book should serve a useful purpose.

Modern Dermatological Therapy. By Thomas H. Sternberg, M.D., and Victor D. Newcomer, M.D. Price, $10. Pp. 520. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1959.

One of the more popular postgraduate seminars in dermatology in this country is that conducted by the University of California in Los Angeles under the direction of Dr. Thomas Sternberg. Prompted by suggestions from students who attend these courses, the material presented last year by the faculty of some twenty-odd teachers from all over the country has been compiled into this book. There are twenty-six chapters devoted to those areas in which laboratory research and therapeutic changes have been greatest in recent years. Among the subjects presented in detail are adrenocorticosteroid therapy, acne, collagen diseases, psychocutaneous disorders, polymorphous light eruptions, psoriasis, microbiologic problems, and others. Missing as a separate unit was a discourse on topical therapy, a feature which usually distinguishes the dermatologist from others treating skin diseases, but therapy was considered in the various chapters.

Although some of the material inevitably lent itself to a more interesting and exciting presentation, practical applications and better understanding of the various conditions can be gleaned from each chapter, and the editors have managed to keep the chapters in balance. It was of more than passing interest to note that the most significant advances were made in disorders investigated by a number of disciplines, though it was heartening to note that dermatologists have contributed significantly in all areas, including both systemic diseases and "purely" dermatologic conditions.

The information is well organized and directed to the practicing physician in a timely and authoritative manner. New drugs, laboratory findings, and other pertinent data are given thorough consideration by a group who both practice and teach dermatology. With its practical, detailed information and fine reference lists, the book constitutes a worthwhile addition to anyone's library.

X-Ray and Radium in Dermatology. By Bernard A. Wansker, M.D. Price, $5. Pp. 114. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1959.

The American Lecture Series has in this book a concise, practical, easy-to-read monograph that should appeal to anyone who practices radiation therapy but especially to the resident in training. It is an outgrowth of notes assembled during the author's training years at Duke University and from the sessions of the American Academy of Dermatology. It reflects excellent training and generously acknowledges the advice and guidance of various experts in the field. The small handbook considers briefly but adequately everything from elementary physics of radiation, through indications for therapy, various techniques, radioisotopes, and radiobiologic mechanisms of the skin. It is a good book to have at hand.

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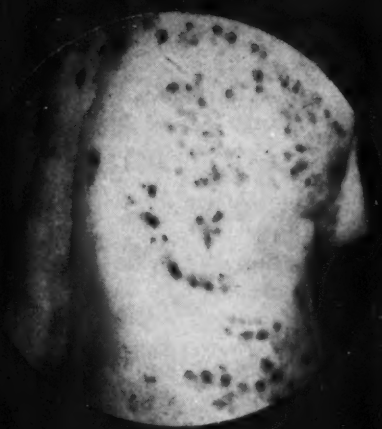
(1) Blank, H., and Roth, F. J.: A.M.A. Arch. Dermat. 79:259 (March) 1959. (2) Williams, D. I.; Marten, R. H., and Sarkany, I.: Lancet 2:1212 (Dec. 6) 1958. (3) Goldfarb, N., and Rosenthal, S. A.: Current M. Digest 26:67 (April) 1959. (4) Wrong, N. M.: Canad. M.A.J. 80:656 (April 15) 1959.



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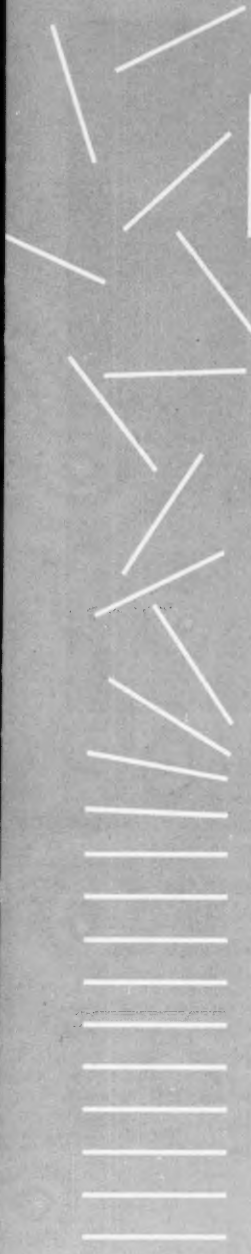

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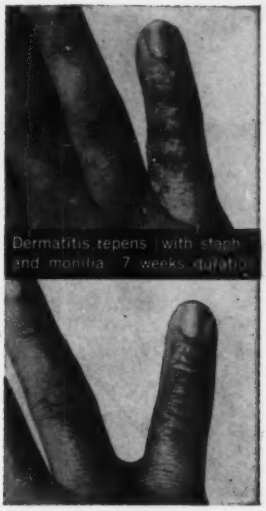

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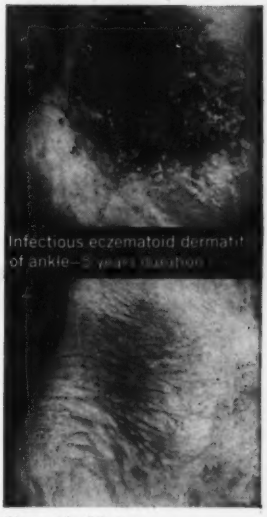

Cleared in 20 days

Mycolog Ointment – containing a new superior topical corticoid Kenalog – reduces inflammation,[3,4] relieves itching,[1,2] and combats or prevents bacterial, monilial and mixed infections.[5-7] It is extremely well tolerated, and assures a rapid, decisive clinical response for most infected dermatoses.

> **"Thirty-one of 38 patients . . . obtained excellent or good control of dermatological lesions . . . (Mycolog) was highly effective, particularly in the management of mixed infections. Several recalcitrant eruptions which had not responded to previous therapy were remarkably responsive to the daily application of this preparation over periods of 2 to 3 weeks."[8]**

For total management of itching, inflamed, infected skin lesions, Mycolog contains triamcinolone acetonide, an outstanding new topical corticoid for prompt, effective relief of itching, burning and inflammation[1-4] – neomycin and gramicidin for powerful antibacterial action[7] – and nystatin for treating or preventing Candida (Monilia) albicans infections.[8,9]

Application: Apply 2 to 3 times daily. Supply: 5 Gm. and 15 Gm. tubes. Each gram supplies 1.0 mg. (0.1%) triamcinolone acetonide, 2.5 mg. neomycin base, 0.25 mg. gramicidin, and 100,000 units nystatin in PLASTIBASE.

References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H., Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith J.G., Jr., Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.

And whatever the topical corticoid need, a suitable Squibb formulation is available—Kenalog-S Lotion—7½ cc. plastic squeeze bottles. Each cc. supplies 1.0 mg. (0.1%) triamcinolone acetonide, 2.5 mg. neomycin base and 0.25 mg. gramicidin. Kenalog Cream, 0.1%—5 Gm. and 15 Gm. tubes. Kenalog Lotion, 0.1%—15 cc. plastic squeeze bottles. Kenalog Ointment, 0.1%—5 Gm. and 15 Gm. tubes.

RELIABILITY

SQUIBB

Squibb Quality — the Priceless Ingredient

"SPECTROCIN"®, "MYCOSTATIN"®, "PLASTIBASE"®, "MYCOLOG" AND "KENALOG" ARE SQUIBB TRADEMARKS

A NEW WIDE-SPECTRUM TOPICAL MICROBICIDE

not an antibiotic . . . not a sulfonamide . . . not a nitrofuran

Triburon

&

Triburon-HC

(containing hydrocortisone 0.5%)

EFFECTIVE EVEN AGAINST ANTIBIOTIC-RESISTANT STRAINS

HIGHLY ACTIVE

■ against most "pathogenic cocci [both staphylococci and streptococci] regardless of their resistance to antibiotics."[1]

■ against pathogens common in skin and wound infections.

VIRTUALLY NONSENSITIZING

■ in more than 4500 stringent, closed-patch sensitivity tests, the incidence of allergic response was less than 2 per cent.[2, 3]

■ in initial clinical studies, only 15 of 1014 patients developed evidence of skin irritation.

MINIMAL RESISTANT ORGANISMS

■ laboratory attempts to develop Triburon-resistant strains produced no substantial change in organism sensitivity.[1]

■ WIDE-SPECTRUM
■ RAPID-ACTING
■ WELL TOLERATED
■ NONSTAINING
■ ODORLESS

DIAGNOSIS AND NO. OF PATIENTS	DURATION OF TREATMENT	RESULTS	ADVERSE REACTIONS
Impetigo contagiosa (50)	Triburon 3-10 days	excellent	none
Ecthyma (24)	Triburon 5-14 days	excellent	none
Pustular folliculitis (16)	Triburon 1-3 weeks	infection controlled	3 complaints of burning
Dermatitis repens (18)	Triburon 1-2 weeks	infection controlled	none
Dermatitis repens (18)	Triburon-HC 1-4 weeks	excellent	none
Secondarily infected eczematous eruption (20)	Triburon 1-2 weeks	infection controlled	none
Secondarily infected eczematous eruption (64)	Triburon-HC 1-4 weeks	excellent	1 complaint of irritation

Chart based on finding of E. Edelson, E. Grunberg and T.V. Morton Jr.

PACKAGES:
Triburon Ointment, 1-oz tubes and 1-lb jars.
Triburon-HC Ointment, 5-Gm and 20-Gm tubes.

REFERENCES: 1. R. J. Schnitzer, E. Grunberg, W. F. DeLorenzo and R. E. Bagdon, to be published.
2. E. Edelson, E. Grunberg and T. V. Morton, Jr., Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959.
3. R. C. V. Robinson and L. E. Harmon, Antibiotics Annual 1958-1959.

TRIBURON™· triclobisonium chloride — N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl) propyl]-N,-N'-dimethyl-1,6-hexanediamine bis (methochloride). ROCHE®

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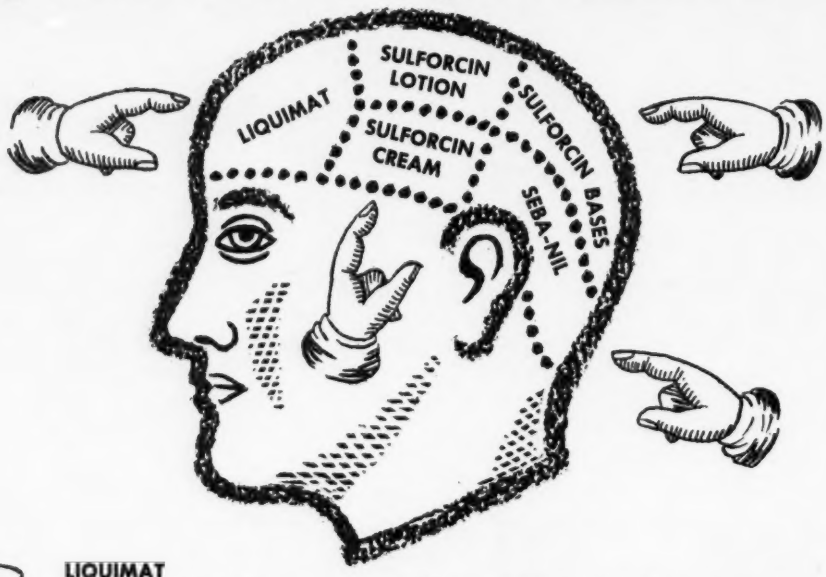

LIQUIMAT

A tinted lotion containing 5% precipitated sulfur for the local treatment of acne. Resorcin, corticosteroids, calamine, phenol, menthol, camphor, betanaphthol and coal tar solution may be added. To individualize prescriptions further, the three shades may be interblended.

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Contains 5% dispersible sulfur and 3% resorcinol monoacetate in a colloid-processed base of citrus pectin. Sulforcin Lotion dries rapidly, holding sulfur securely to the skin. Non-sticky, non-greasy, non-staining.

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Clinical studies prove conclusively that very oily skins respond more rapidly to acne therapy when cleansed with Seba-Nil rather than soap and water. Seba-Nil contains organic solvents and a mild, non-ionic detergent which make it more efficient than soap and water in preparing oily skin for medication.

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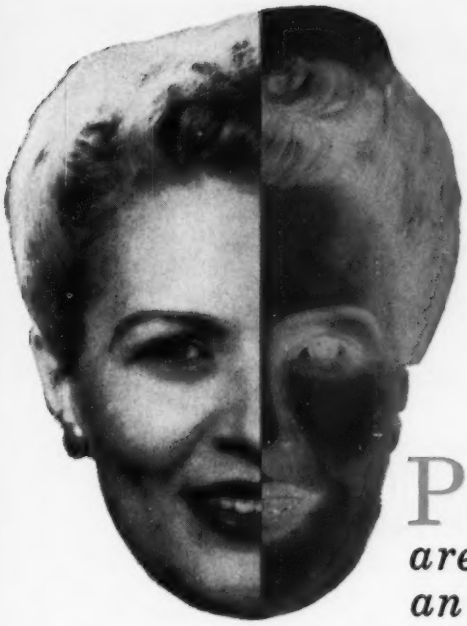

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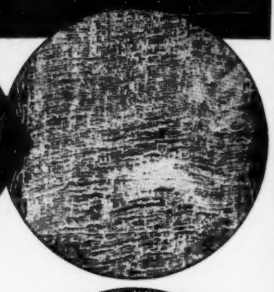

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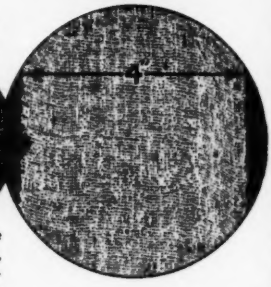

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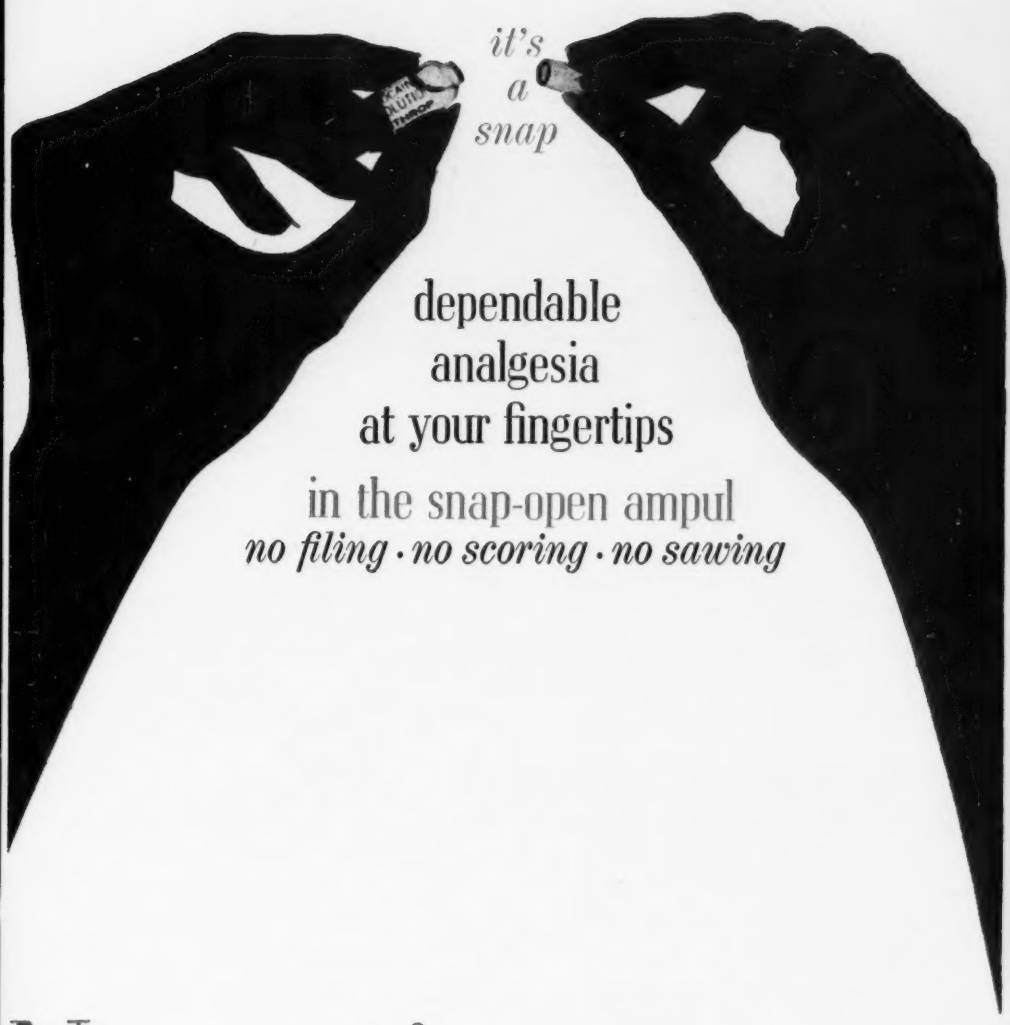

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Reference: Gross E. R. and Wright C. S., A. M. A. Archives of Dermatology, 78:92, July, 1958

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"The importance of a measure designed to return the pH of the skin quickly to its normal values after exposure to soap and alkalies is amply borne out..."

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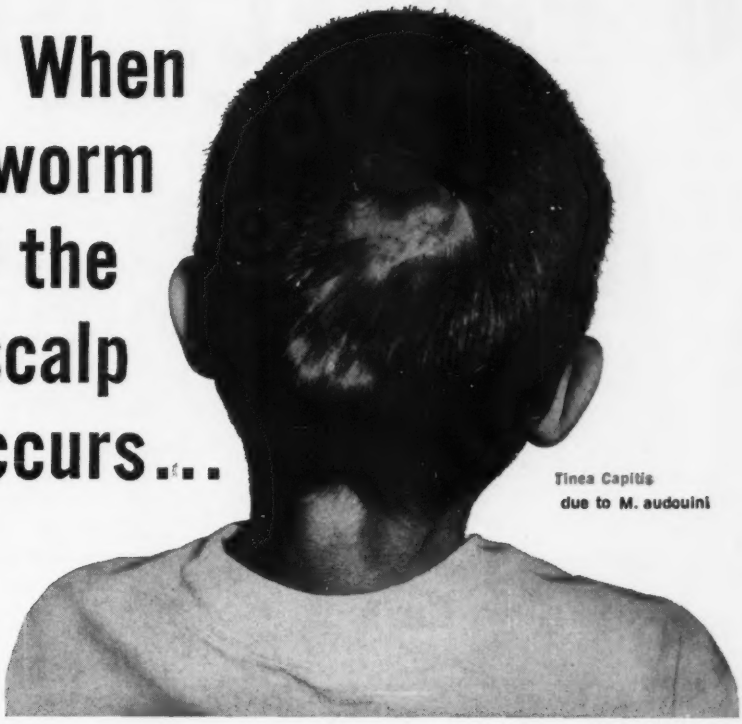
When ringworm of the scalp occurs...



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. . . topical antifungal therapy is recommended as immediate treatment. Prompt use of Salundek will destroy accessible spores and form a protective coating, reducing the likelihood of spread of the disease to other areas of the scalp, or to other children.

*New Dosage Form, Salundek Solution** – It is supplied in 3-ounce bottles with a controlled flow applicator cap. Now there is a choice that will lead to better patient cooperation during the treatment of this stubborn disease.

Many investigators have reported that the ointment and the solution have the same high percentage of cures, obtained in an average of 12 to 16 weeks.

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*In the presence of open lesions, the use of the ointment may be preferred at first since the base of the solution causes occasional transient stinging. Avoid contact with the eyes.

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1. Shaw, J. M., and Crowe, F. W.: Skin Protective Ointments. Arch. Dermat. & Syph. 71: 379, 1955.

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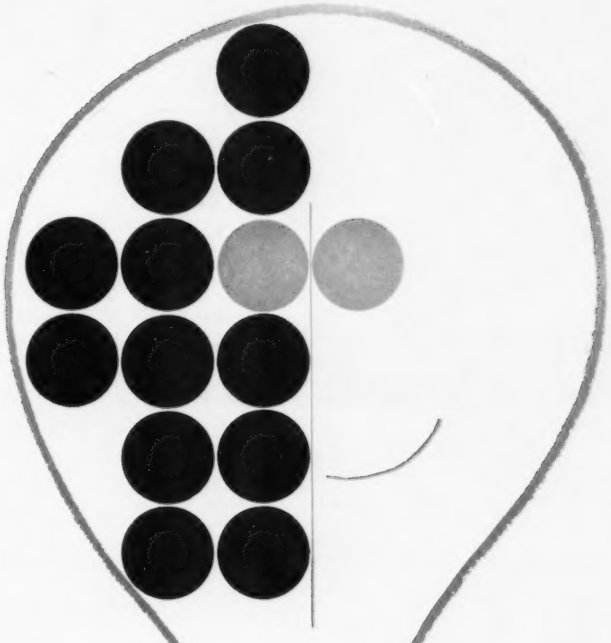

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References: 1. *Cahn, M. M.: The use of tranquilizing drugs in dermatology. J. Albert Einstein M. Center* **4**:*161, Sept. 1956.*
2. *LeVan, P. and Wright, E. T.: Use of tranquilizers in diseases of the skin – A preliminary report. California Med.* **85**:*87, Aug. 1956.*
3. *Sokoloff, O. J.: Meprobamate (Miltown) as adjunct in treatment of anogenital pruritus. A.M.A. Arch. Dermat. & Syph.* **74**:*393, Oct. 1956.*

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*Diseases of the Colon & Rectum, Vol. 1, No. 5, Sept.-Oct. 1958.

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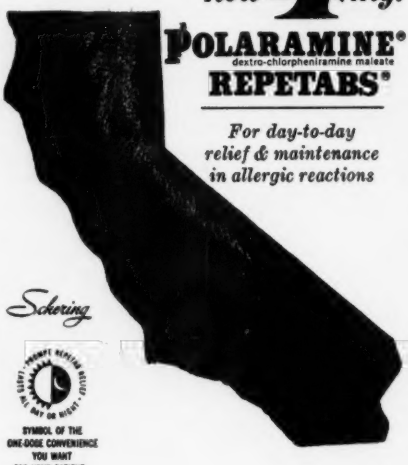

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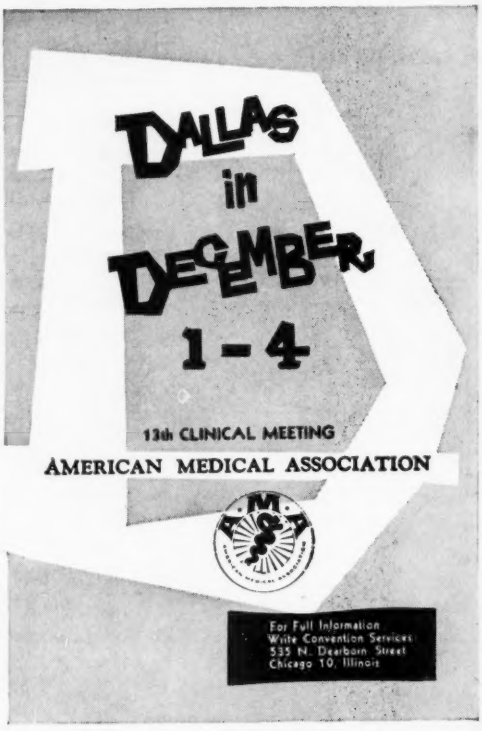

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*Zakon, S. J., et al.: Arch. Dermat. & Syph. 56:499, 1947; abstracted in Birmingham, D. J., and Campbell, P. C., Jr.: Occupational and Related Dermatoses, U. S. Public Health Service Publication No. 364, 1954.

in acute dermatoses

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1. Welsh, A. L., and Eds, M.: J.A.M.A. 155:158, 1954.

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Supplied: Spray container, 85 Gm.

Additional Clinical Publications on Tarcortin:

Clyman, S. G.: Postgrad. Med. 21:308, 1957 • Bielberg, J.: J. M. Soc. New Jersey 53:37, 1956 • Abrams, B. P., and Shaw, C.: Clin. Med. 3:439, 1956 • Bielberg, J.: Am. Practitioner 8:1404, 1957

TARCORTIN®

Cream & Lotion

Hydrocortisone 0.5% and Special Coal Tar Extract 5% (TARBONIDE®) in a greaseless, stainless vanishing base. Cream: 7 gm. and 1 oz. tubes. Lotion: Plastic squeeze bottles, ½ oz.

ALSO AVAILABLE: FOR DRY SCALY ECZEMAS, AND WHEN INFECTION IS PRESENT OR ANTICIPATED

NEO-TARCORTIN®

Ointment

Hydrocortisone 0.5%, Neomycin (as Sulphate) 0.35% and Special Coal Tar Extract 5%. In tubes of 7 gm. and 1 oz.

REED & CARNRICK Kenilworth, New Jersey

TO TREAT

ITCHY, SCALY SCALP

WHICH TENDS TO DRYNESS

sebulex®

ANTISEBORRHEIC SHAMPOO

WESTWOOD PHARMACEUTICALS, Buffalo 13, New York

sebulex®

a therapeutic shampoo for the treatment of itchy, scaly scalp which tends to dryness

Stops itching, removes loose dandruff and crusty, matted layers of scales from the scalp through the effective cleansing, penetrating and antiseborrheic actions of *Sebulytic*®, a combination of anionic surface-active cleansers and wetting agents. The antiseborrheic qualities of Sebulytic are further enhanced with the addition of sulfur and salicylic acid. Hexachlorophene provides antibacterial action.

Prevents excessive drying of the scalp through the action of *Kerohydric*™, a crystal-clear, dewaxed fraction derived from lanolin. Kerohydric also leaves the hair soft and more manageable after shampooing.

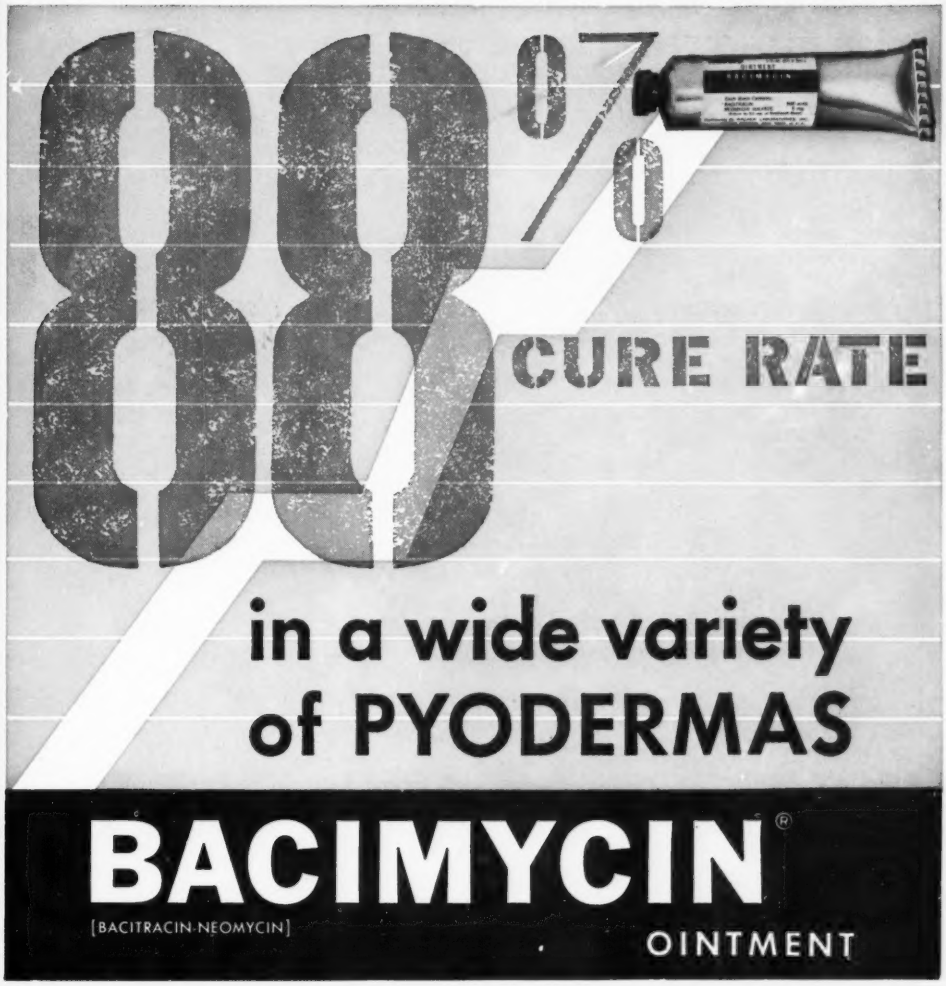
Sebulex is cosmetically elegant. Sebulex meets the up-to-date "cosmetic" requirements for a therapeutic shampoo. It has a smooth, lotion-like texture, an appealing pastel green color, delightful fragrance and produces an abundant lather. Patients like shampooing with Sebulex.

Sebulex does not contain any toxic metallic materials. Thus, it can be used for a prolonged period of time without danger of systemic toxic effects.

Sebulex contains a mixture of anionic surface-active cleansers and wetting agents (Sebulytic). These agents consist of sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate, and sodium dioctyl sulfosuccinate. Sebulex also contains Kerohydric, a crystal-clear, dewaxed fraction of lanolin; sulfur 2%, salicylic acid 2% and hexachlorophene 1%.

Available: In plastic bottles of 4 oz. *Write for samples.*

WESTWOOD PHARMACEUTICALS, Buffalo 13, New York



a first choice for dual antibiotic therapy

In a recent study[1] of 53 patients with various types of pyodermas, the use of BACIMYCIN Ointment "... resulted in a cure rate of 88%...." Impetigo, infectious eczematoid dermatitis, atopic eczema, secondary infections superimposed on dermatitis venenata, and folliculitis were among the common skin infections that showed marked improvement with BACIMYCIN therapy.

BACIMYCIN rarely produces sensitization or primary irritation.

Supplied in ½ oz. tubes for prescriptions; in 100 gm. jars for hospital use; in ⅛ oz. tubes for ophthalmic use. Also supplied as BACIMYCIN with Hydrocortisone, ⅛ oz. tube with applicator tip.

Literature and samples on request.

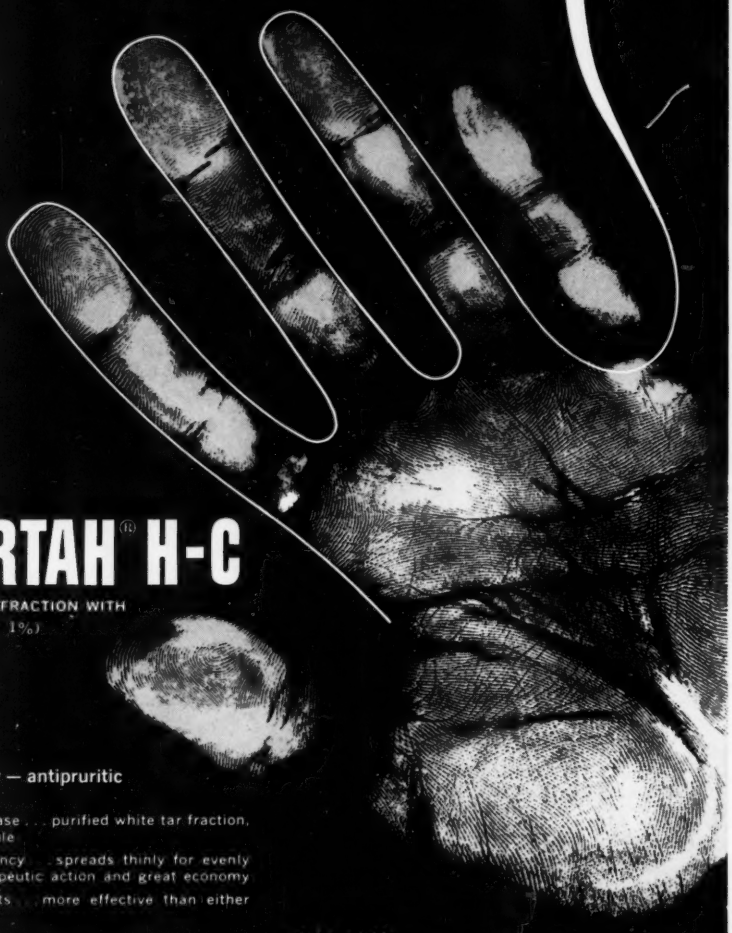
1. Greenhouse, J. M., and Ryle, W. C.: A.M.A. Arch. Dermat. & Syph. 69:366 (March) 1954.

Walker **LABORATORIES, INC.** MOUNT VERNON, NEW YORK

spreads

THINLY · EVENLY · ECONOMICALLY

in acute dermatologic conditions



SUPERTAH® H-C

(1.25% COAL TAR FRACTION WITH HYDROCORTISONE 1%)

antiinflammatory — antipruritic

- water miscible base . . . purified white tar fraction, stainless, washable
- maximum efficiency . . . spreads thinly for evenly distributed therapeutic action and great economy
- enhanced benefits . . . more effective than either agent alone
- excellent response . . . deep penetration to source of inflammation

supplied: ½-oz. tube

also available:

SUPERTAH Ointment (1½-oz. tube)
provides the therapeutic effectiveness of time-proved tar medication

SUPERTAH S/S (with salicylic acid and sulfur; 1½-oz. tube)
for keratolytic action

All Supertah preparations are made with refined natural coal tar fraction.

established in 1905

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